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Presenter Disclosure
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The following relationships exist related to this presentation:

No Relationships to Disclose



Preparing for an FDA Inspection

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Objectives

- Describe when FDA inspects clinical sites and sponsors
- Explain what happens during an FDA inspection
- Explain what happens after the inspection
- Discuss violations seen 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 NDA /BLA / PMA
- Referrals from Center staff
- Referrals from other parts of FDA
- Complaints from sponsors, IRBs, and consumers
- Surveillance of ongoing studies

Profile of Sponsors for CBER Active INDs

(as of 3/12/10)

Cell and Gene INDs	#
Total	832
Individual	415
Commercial	273
Hospital/Medical Center/University	98
Government (NIH, CDC,...)	43
“Other” (COGs, nonprofits...)	3

Profile of CBER's Inspections of Cell and Gene Therapies

	Total	301
Clinical investigator		216
Sponsor/monitor		45
Sponsor/investigator		18
GLP + GMP + IRB		22

*All inspections since we started tracking product type

Why Did FDA Conduct These Cell and Gene Therapy Inspections?

Surveillance	175
Complaints	75
Marketing applications	15

The other inspections were requested by the product reviewers, initiated by the FDA District Office, or the reason was not tracked.

Are You Ready for an Inspection?

Ideally, all of your records are present, well organized, legible, and complete.

No special preparation is necessary.

FDA Inspection Nuts & Bolts

-- *Before* --

- With rare exceptions, inspections are preannounced (scheduled).
- The routine notification is 3-5 working days.
- Inspections may be conducted without prior notice or with minimal (1 day) notice.
- Inspections are performed by FDA District Offices by specially-trained investigators

Center reviewers may participate

FDA Inspection Nuts & Bolts

-- *Before* --

- Have available:
 - All study documents
 - Person knowledgeable about the study
 - A place to review records
 - Access to a photocopier
- FDA investigator follows compliance program
 - 7348.811 (clinical investigator inspection)
 - 7348.810 (sponsor / monitor / CRO inspection)

<http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm>

The Inspection Begins

- FDA investigator will show credentials
 - You may ask to write down the information on the credentials & obtain the badge number of the field investigator
 - You may not photocopy the credentials or take them away from the FDA officer
- FDA investigator will issue a Notice of Inspection (Form FDA 482)
 - Shows FDA District contact information
 - Issued to responsible individual
 - Identifies firm to be inspected
 - Shows date and time issued
 - States FDA's authority to inspect

- Interview: who did what, and how
- Review source documents and case report forms to assess compliance in five major areas:
 - Protection of human subjects
 - Protocol compliance
 - Adverse event reporting
 - Data verification, especially the primary endpoints
 - Drug accountability
- Closing discussion & issue Form FDA 483, Inspectional Observations

Where is the Term "Source Data" Defined?

NOT defined in 312 or 812

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 Data Quality = ALCOA

Attributable

Legible/readable

Contemporaneous

Original

Accurate

Common Questions for FDA

Can case report forms be source documents?

Yes – protocol should specify how data are to be captured and records are to be maintained.

Are diaries, questionnaires, and photos subject to inspection?

Yes –these need to be maintained by investigator per 21 CFR 312.62(c)

FDA Inspection Nuts & Bolts

-- Exit Interview --

- Conclusion of inspection
 - Usually scheduled 1-2 days before
 - Most responsible persons should attend
- May issue a Form FDA-483
- Discuss inspection findings
- Verbal response to FDA-483

Form FDA 483, Inspectional Observations

- Represent the observations of the FDA investigator
- Violations of regulations, not guidance
- Written communication of violations that the sponsor or investigator + staff were not able to adequately address during the inspection.
- Discussion points: Observations communicated verbally.

End of the Inspection

Discussion of findings

- You will be asked at the time of the exit interview to respond* to the 483 points
 - may choose not to respond
 - may dispute any or all points
 - may agree with any or all points
 - may suggest corrective actions

* responses included in the Establishment Inspection Report
- You are not required to respond **in writing** to the 483 at the time of the inspection or afterward.

- You may respond in a letter - send to address on the Form FDA-483.
- May also call the FDA investigator for the Center address and send the letter there
- Letters received by FDA within 15 days will be considered prior to issuing a warning letter
- Take the findings seriously
- Your detailed description of your completed and intended corrective actions may render further action unnecessary.

What Happens Next?

- The FDA investigator writes the inspection report regardless of whether a Form FDA 483 was issued.
- The written report is the Establishment Inspection Report (EIR).
- Field investigator forwards EIR to the Center
- Center evaluates the report and exhibits collected

The Center Follows Up

- The Center evaluates the report, and determines if corrective actions are needed.
- Classifications
 - NAI – No Action Indicated
 - VAI – Voluntary Action Indicated
 - OAI – Official Action Indicated
- The Center will write a letter following most inspections
- In most cases the letter will close the inspection
- After the inspection is closed a copy of the written inspection report is sent to you.

Most Common Investigator Violations

Failure to follow the protocol

example: Required testing is incomplete

Recordkeeping errors

Informed consent problems

Most Significant Violations

- Enrollment of ineligible subjects
- Violation of protocol affecting 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

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?

Did the sponsor report the problems to FDA?

...indicate that other studies at that site might be impacted? *investigator problems*

Possible Actions for OAIs

Actions for Inspected Party

- Warning letter
 - * There might be another inspection to confirm that the promised corrections were implemented
- Initiate clinical investigator disqualification
- Referral of FDA Office of Criminal Investigations
- Injunction
- Seizure
- Prosecution
 - Debarment if convicted of felony on FDA-related charges

Possible Actions for OAI

Actions on Applications

- Clinical hold of a drug/biologic study (IND)
- Disapprove a device study (IDE)
- Reject the Data ✍ *Do another study*

- Terminate IND / Withdraw IDE
- Withdraw Approval of marketing approval / revoke license
- Application Integrity Policy

FDA's Electronic Freedom of Information Reading Room

[http://www.fda.gov/RegulatoryInformation/foi/
ElectronicReadingRoom/default.htm](http://www.fda.gov/RegulatoryInformation/foi/ElectronicReadingRoom/default.htm)

Warning letters

Clinical Investigators

Letters about pending disqualification actions

Disqualified and restricted CIs

Presiding officer decisions

Compliance References

<http://www.fda.gov/ICECI/Inspections/default.htm>

Regulatory Procedures Manual

warning letters, untitled letters, judicial actions

Application Integrity Policy

Debarment list

Bioresearch Monitoring compliance programs

[http://www.fda.gov/ScienceResearch/SpecialTopics/Running
ClinicalTrials/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm)

Good Clinical Practice references

Suggestions 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 to 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

Inappropriate delegation to subinvestigators

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

**** How many miles (or states!) away ????

Sponsor must ensure that CI controls the study
***** BIG challenge for study coordinators and support staff

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 change the protocol

Suggestions to Prevent Noncompliance - *During* -

- Verify that delegated duties are performed
- Work with monitors
- Correct small problems before they grow

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)

True or False???

Clinical investigator: “I’m only doing phase 1 and 2 studies – I’ll never be inspected by FDA.”

True or False???

Clinical investigator: "I'm only doing phase 1 and 2 studies – I'll never be inspected by FDA."

FALSE

Clinical investigators of studies in all phases may (and are) inspected by FDA....

And ALL GCP regulations apply.

True or False???

If FDA decides to inspect me, I've done something wrong.

True or False???

If FDA decides to inspect me, I've done something wrong.

Answer: **Maybe**

True or False???

If I get a 483, this means I will get a Warning Letter.

True or False???

Q3. If I get a 483, this means I will get a Warning Letter.

Answer: **Probably not**

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