

FDA INSPECTION OF AN IND STUDY

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OVERVIEW

The investigational new drug/investigational device exemption (IND/IDE) case studies provide education and guidance on regulatory and ethical issues associated with IND/IDE research and submissions to the Food and Drug Administration (FDA). Each follows a standard format of: 1) fact pattern, 2) regulatory issues, and 3) a risk/benefit analysis and risk management options.

The case studies are intended to aid IRB Administrators, Human Research Protection Program (HRPP) staff, and investigators when reviewing or conducting IND and IDE research. They can be used as a tool for: 1) training individuals in human subjects research involving investigational drugs/devices, 2) developing reviewer checklists/worksheets, and 3) designing research projects.

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CASE STUDY

SCENARIO/FACT PATTERN, PART 1:

Dr. Sosa is the Principal Investigator (PI) and Sponsor-Investigator of an approved research protocol to study the effectiveness of an investigational drug in patients with Asthma. Dr. Sosa has an Investigational New Drug (IND) Application for this product and has enrolled several subjects to date. There were a few instances where he deviated from the approved protocol without reporting. For example, two subjects signed a version of the consent form that has not been reviewed and approved by the IRB at his institution. Two other subjects called the study coordinator and complained that they developed a severe skin rash from the study drug. Developing a skin rash was not listed as an expected side effect in the informed consent form. The research team did not report the development of the skin rash in these two subjects to the IRB or the FDA. Additionally, though the protocol stated that the research study drug should be stored in a locked cabinet, the PI is unable to account for several packages of the research study drug.

The FDA received a complaint regarding this site via phone. Given this, the FDA notified Dr. Sosa on a Friday afternoon that there would be an FDA inspection beginning early the following week. How should Dr. Sosa prepare for the FDA inspection?

Regulatory Issues:

After notification of the FDA inspection, here is what Dr. Sosa should prepare:

- **Notify his institution that an FDA inspection will be occurring.** The FDA inspector generally communicates directly with the principal investigator, not with the institutional official or representative. Therefore, it is critical that the PI notify the appropriate parties at his institution. Some institutions will have a particular department or person that coordinates support for the investigator during an FDA inspection (e.g. institutional liaison) and can assist with these communications. The PI should ensure that appropriate institutional offices and personnel are notified. Offices/personnel may include:
 - Institutional Review Board (IRB)
 - Institutional Official at the hospital or university
 - Research Compliance Office
 - Quality Improvement Group/Program (if this is different than the Compliance Office)
 - Research Pharmacy or laboratory (if applicable)
 - If there are institutional personnel who can help during the inspection preparation or during the FDA inspection (such as the exit interview) with responses to institutional policy related questions, Dr. Sosa should work with this resource.
- To the best of the PI's ability, given the time available before the FDA inspection, **review study documents and report any protocol deviations or adverse events** discovered to the appropriate parties (e.g., IRB, FDA, Sponsor) including corrective action.
- **Ensure all study documents are available and organized**, including subject files, regulatory documents and informed consent forms (including electronic records if applicable). Examples of study documents include but are not limited to:
 - Protocol (original and any revisions)
 - Informed consent forms
 - Documentation of Qualifications for all study staff (e.g. CV, medical licensures)
 - Investigator agreements and financial disclosures
 - Documentation of any required training for study staff
 - Documentation of appropriate delegation of tasks (e.g. delegation log)
 - Correspondence with Sponsor
 - CRO or vendor agreements (if applicable)
 - Drug Accountability for the investigational product, including shipping records and disposition of unused investigational product
 - Monitoring plan & reports
 - Study subject records (CRFs, diaries, etc.)
 - Adverse event reports
 - Standard Operating Procedures for conduct of study (e.g. operations, investigational product safety, monitoring, regulatory, quality assurance, product accountability, training, and non-compliance)
- **Ensure the availability of study personnel** that the FDA may want to interview during the inspection
- **Secure a quiet area** for the FDA inspector(s) to conduct the inspection with access to the internet and a photocopier

- **Review internal policies and SOPs** to ensure that they are up to date (if possible) and staff are aware of them
- Ensure all study personnel are up to date on the latest SOPs for the department

What issues does part 1 raise regarding Dr. Sosa's responsibilities as a sponsor-investigator?

- Failure to obtain informed consent from subjects (21 CFR 50.20) since the subjects consented to participate, but did not sign the appropriate version of the consent
- Failure to document and report adverse events [21 CFR 312.64 (b)]. The researcher should have documented the rash and notified the IRB (and FDA) promptly if the rash is considered serious, related, and expected.
- Failure to ensure maintenance of study drug accountability records [21 CFR 312.62(a)]
- Failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]

Part 2:

The inspection concluded with the FDA Investigator conducting an exit interview with Dr. Sosa. The inspector issued a Form FDA 483 (Inspectional Observations for significant deviations from the regulations) to the researcher, which included the following deficiencies:

- Failure to obtain informed consent from subjects (21 CFR 50.20)
- Failure to document and report adverse events [21 CFR 312.64 (b)]
- Failure to ensure maintenance of study drug accountability records [21 CFR 312.62(a)]
- Failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]

Written Response

The PI may respond to the 483 observations orally during the exit interview or in writing, following conclusion of the inspection. The written response should be directed to the FDA District Office listed in the 483 within 15 business days. The written response should include:

- An evaluation of the extent of the problem
- Assessment of the root cause of the problem
- Any corrective actions
 - Not just a statement that the PI will correct or plan to correct the problem, but a clear and detailed plan to correct the issues.
 - What will be corrected?
 - How will it be completed?
 - Is the problem systemic?
 - What actions have been taken thus far?
- What preventive steps are being taken to prevent recurrence of the problem in future studies?
- Timeframe for corrective action
- Supporting documentation

The PI must develop a **corrective and preventive action plan** to correct the FDA findings. Note that the PI should seek guidance from the IRB as needed and also ensure that all corrective actions adhere to IRB policy as well. Possible corrective actions include:

Informed Consent:

- Asking research subjects to sign the currently approved consent form so as to be re-consented
- Make sure that the correct version of the consent form/document is obtained and documented in compliance with study protocol and regulatory requirements

Adverse Events/Patient Safety and Accountability

- Report the adverse events in compliance with the study protocol, IRB requirements, and regulations within the timeframe
- Ensure that the drug accountability logs are completed with the study drug, subject, date, time, and individual removing from the central account
- Review the protocol deviation and study difference between what study protocols require and what was done at the site? Document what happened and evaluate if sponsor should be contacted about evaluating further participation.

Corrective Action Plan (CAPA)

- The CAPA plan must be documented and the results of the CAPA activities evaluated to see if they were effective. The documentation will need to be available to show investigators who may find this issue in the future
- Retraining of study staff on informed consent and drug accountability
- Request periodic internal audits or monitoring to ensure that the corrective action plan is implemented
- If SOPs are not in place, develop, implement, and maintain specific and accurate SOPs (make it specific for drug accountability)

REFERENCE(S):

[Title 21: Food and Drugs; Part 312—Investigational New Drug Application](#)

21 CFR 312.30 – Protocol amendments.

21 CFR 312.32 – IND safety reporting.

21 CFR 312.53 – Selecting investigators and monitors.

21 CFR 312.55 – Informing investigators.

21 CFR 312.56 – Review of ongoing investigations.

21 CFR 312.57 – Record keeping and record retention.

21 CFR 312.58 – Inspection of sponsor's records and reports.

21 CFR 312.59 – Disposition of unused supply of investigational drug.

21 CFR 312.60 – General responsibilities of investigators.

21 CFR 312.61 – Control of the investigational drug.

21 CFR 312.62 – Investigator record keeping and record retention.

21 CFR 312.64 - Investigator Reports

21 CFR 312.66 – Assurance of IRB review.

Title 21: Food and Drugs; Part 50.20 Protection of Human Subjects