FDA INSPECTIONS
NEED NOT BE STRESSFUL

A Complion Feature Article

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Introduction

As a stakeholder in a research facility the prospect of an inspection by the US Food and Drug Administration (FDA) may elevate your blood pressure and induce feelings of panic. But according to Dr. Harvey Arbit, "the FDA inspection process should go quite smoothly if you're doing everything right." Still nervous? Don't be.

Dr. Arbit is the president of Arbit Consulting and an adjunct professor at the University of Minnesota College of Pharmacy. He holds a PharmD from Duquesne University, an MBA from Northern Illinois University, and a BS, Pharmacy from the Albany College of Pharmacy of Union University. His professional experience spans more than 30 years in the pharmaceutical and medical device industries.

Compliance Program Guidance Manuals

Getting it right means starting off with the right information. Dr. Arbit recommends resources offered by the FDA itself. These include a series of compliance program guidance manuals that provide insight into the FDA inspection program and how FDA personnel are trained.

Listed below are three compliance program guidance manuals, one for sponsors, contract research organizations and monitors, one for clinical investigators, the third for institutional review boards.

- 7348.810 Sponsors, Contract Research Organizations and Monitors
  - How sponsors assure validity of data from investigators
  - Adherence to applicable regulations
- 7348.811 Clinical Investigators and Sponsor Investigators
  - Quality and integrity of data submitted to FDA to support safety and efficacy
  - Protection of human rights
  - Compliance with regulations
- 7348.809 Institutional Review Boards
  - Protect the rights, safety, and welfare of subjects
  - Accuracy and reliability of data submitted to FDA
  - Compliance of regulations

In addition, the FDA also offers *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors*. Documents in this series include:

- FDA Inspections of Clinical Investigators
- FDA Institutional Review Board Inspections

These information sheets offer information on when and how inspections are conducted, on what is examined during an inspection, and on what happens after an inspection. Dr Arbit suggests that those involved with the clinic investigator or the institutional review board will find value in these documents.

Bioreseach Monitoring Program (BIMO)

In 1977 the FDA established the Bioresearch Monitoring Program in order to ensure that the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical trials are protected. BIMO also verifies the accuracy and reliability of clinical data submitted to the FDA in support of research or marketing applications, and assesses compliance with statutory requirements and FDA regulations governing the conduct of clinical trials. Under the BIMO program the FDA can perform inspection visits to the following:

- Clinical Investigators (PIs)
- Sponsors
- Monitors
- Contract Research Organizations (CROs)
- Institutional Review Boards (IRBs)
- Non-clinical (animal) laboratories
- Bio-equivalence analytical laboratories

"If you happen to be a sponsor investigator, then you double your chance of the FDA coming in," says Dr Arbit. "If you are a monitoring organization of an IRB, the FDA has jurisdiction to come in and do an inspection."

Most Common CI Deficiencies

Per Dr. Arbit, the most common deficiencies noted during FDA inspections of clinical investigators include:

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate record keeping

- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection - failure to report AEs and informed consent issues

Most Common Sponsor and Monitor Deficiencies

Similarly, among sponsors and monitors FDA inspections most often reveal the following problems:

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

The most common deficiency is inadequate monitoring. "You need to keep in mind that monitoring under an IND or an IDE is a sponsor obligation," explains Dr. Arbit. "If you are a sponsor investigator then you also have that sponsor obligation to meet." Monitors need to insure compliance with the protocol. "Their job is to bring investigators into compliance," says Dr. Arbit. "If they cannot bring them into compliance then it is their job to discontinue them from the study."

Most Common IRB Deficiencies

FDA inspections also reveal the following deficiencies among institutional review boards:

- Inadequate initial / continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate meeting minutes
- Quorum issues
- Subpart D issues (records and reports)
- Inadequate communication with CI/institution
- Lack of correct SR/NSR determination (specific to devices)

Clinical Investigator Inspections

Clinical investigator inspections are intended to determine whether clinical investigators are conducting the clinical studies in compliance with applicable statutory and regulatory requirements. The clinical investigators who conduct FDA regulated investigations are required to permit FDA inspectors to access, copy and verify any records or reports made by the clinical investigator with regard to, among other records, the disposition of the investigational product and subject's case histories.

Inspections (21 CFR 812.145; 312.58; 312.68)

- Sponsor or investigator shall permit FDA employees to enter and inspect the establishment and records.
- Sponsor, IRB, or investigator shall permit FDA employees to inspect and copy all records.
- Investigator shall permit FDA employee to inspect and copy records that identify subjects.

The Code of Federal Regulations Title 21, in Section 812 for IDEs and Section 312 for INDs, addresses inspections. Based on these regulations a sponsor or investigator must permit FDA employees to enter and inspect the establishment and records. The regulations further state that the IRB sponsor or the investigator must permit FDA employees to inspect and copy records that identify subjects. "You can't say to the FDA investigator, 'HIPAA prevents me from showing these records because they have patient's names on them,'" Dr. Arbit explains. "In this case, HIPAA does not apply."

Announced and Unannounced Inspections

The purpose of FDA inspections is to verify the accuracy and reliability of data submitted to the agency. Inspections may be triggered by a variety of events:

- Study-related complaints to the agency
- In response to sponsor concerns
- Upon termination of the clinical site
- At the request of an FDA review division

The FDA may order an inspection during ongoing clinical trials in order to provide a real-time assessment of the investigator's conduct of the trial and of the protection of human subjects.

Inspections may also occur in relation to certain classes of investigational products that the FDA has identified as being of special interest in its current work plan. For example, a targeted inspection may be ordered based on current public health concerns.

Some inspections are announced. Others are not. "It depends on the circumstances," according to Dr. Arbit. "If the FDA is coming in to do a routine inspection based on the sponsor being ready to submit their marketing application, the FDA may want to verify that the data that the investigator sees matches the data that the sponsor has submitted to the FDA. That will probably be an announced inspection."

Other inspections may be the result of a complaint to the agency about the conduct of a study at a particular investigational site. For example, an inspection may be the result of a patient's accusation of improper treatment during the research process. An inspection might also result from accusations from a disgruntled employee. "The FDA is going to come in, probably unannounced, to see what's going on and see whether those complaints are valid," Dr. Arbit says. The specifics of the situation determine whether the FDA comes in announced or unannounced.

Inspection Standard Operating Procedures

Do you have a standard operating procedure (SOP) for FDA inspections? "SOPs are always an important part of regulatory affairs." says Dr. Arbit. "If you don't have one, perhaps you should. I think it's important." Why? As Dr. Arbit explains, "The SOP indicates who does what." For that reason, training on the SOP is important to ensure that "everybody knows what their role is and they know how to perform it."

The FDA Inspection Process

Let’s take a close look at the FDA inspection process. To do that we'll divide the process into four steps.

At the Start

The process begins when the FDA investigator arrives at the research site. The investigator will present his/her credentials and issue a completed Form FDA 482 (Notice of Inspection) to the clinical investigator or the appropriate member of the study staff.

"Keep in mind that the FDA is authorized at reasonable times to access, inspect and copy records," advises Dr. Arbit. For example, if normal business hours for your research clinic are 8:00 a.m. to 5:00 p.m., and those are the hours during which you recruit and care for patients in the study, regulations require that you provide access, if the FDA inspector comes knocking. But regulations also prevent after-hours inspections. "If the FDA were to show up at 10:00 p.m., that's unreasonable because you're not operating," Dr. Arbit points out. "On the other hand, if your clinic is open 24/7, and you're recruiting patients 24/7, and the FDA wants to come in at 10:00 p.m., you should be prepared. Someone should be there to greet the FDA inspector and to make some phone calls to bring the staff in for an inspection."

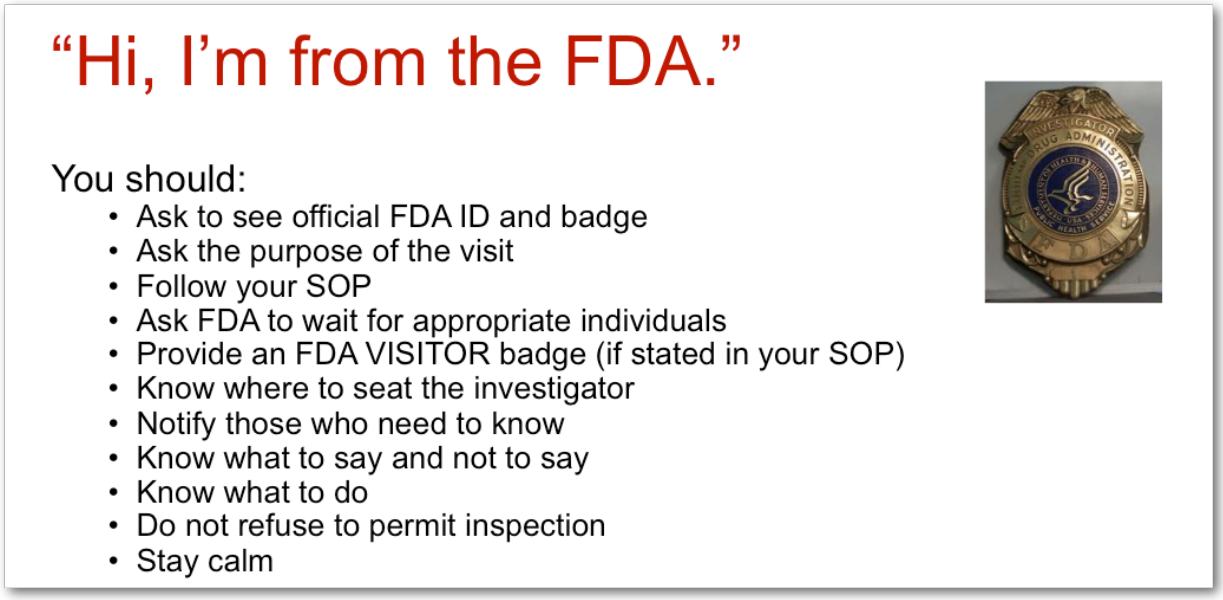


Figure 1

FDA inspectors carry badges. If the inspector does not show you his/her badge on arrival, ask to see it and their photo ID. If the inspector has not informed you of the purpose of the visit, ask. These actions should be covered in your SOP, so that all staff members likely to be involved in an inspection know exactly what they are supposed to do. "If you have an SOP, follow your SOP," Dr. Arbit says.

On the arrival of the inspector, make sure you notify stakeholders. These may include your department head, university general counsel, or vice president of research -- anyone who needs to know about or be involved in the inspection. "If you need to wait for other individuals to arrive, ask the FDA to sit and wait for those individuals," Dr Arbit says.

While waiting for the arrival of other staff members, seat the investigator in a private area. Take care not to seat the inspector near staff members who may be working and chatting about other investigations. It is important to be in control of what the inspector sees and hears.

If your SOP requires the FDA investigator to wear an FDA visitor badge, make sure you provide one. "But don't give them a badge if you don't have an SOP that says you're going to give them a badge," Dr. Arbit warns. "They may ask you, 'Why am I wearing a badge when nobody else is wearing a badge?'"

Preparation is key. "Know what to say and not to say" Dr. Arbit says. "Know what to do, and do not refuse to permit inspection. And stay calm. If you adhere to your SOPs, the regulations, and the protocol, there should be nothing to worry about."

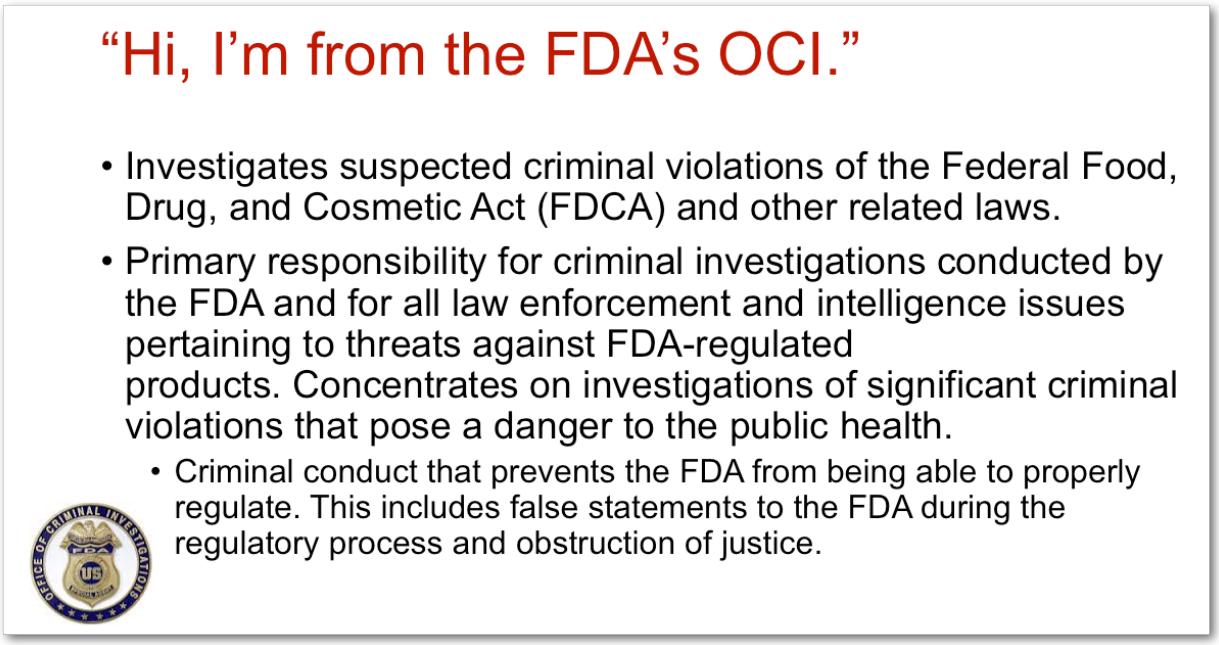


Figure 2

Under certain circumstances your visitor from the FDA may represent the agency's Office of Criminal Investigation. In such cases the routine is similar to that of a regular investigation -- with a significant difference. "They're in to investigate possible criminal conduct," Dr. Arbit says. "If they do arrive, you will then want to notify legal counsel."

At this point, if the inspector has presented the proper credentials (badge, photo ID, and Form FDA 482), and if your stakeholders have arrived, the inspection can begin.

During the Inspection

The inspector will start with some standard questions. "They'll probably ask about how the investigator became involved in this research," says Dr. Arbit. "They're going to ask about the responsibilities of all the team members, how results are recorded, about the control and disposition of test articles, and about how randomization is done."

Expectations During an Inspection

- What the PI Should Expect from the FDA
- Discuss all observations
- Minimize surprises, errors, misunderstandings
- What the FDA Expects of the PI
- Ask Questions About Observations
- Request Clarification
- Confirmation of corrections

"During the inspection the principal investigator should expect the FDA to discuss all observations as they occur, or at least discuss them on a daily basis." says Dr. Arbit. "This will minimize surprises, errors, and misunderstandings."

Conversely, the FDA inspector has expectations of the principal investigator. "Ask questions about any observations," Dr. Arbit says. "Request clarification, and indicate any corrections that have been or will be made while the investigator is still there."

Throughout this exchange clear communication is essential.

Team Approach

Leader

- Primary contact for FDA inspector
- Primary responder to all questions
- Inspection coordinator
- Note taker

Runner

- Document retriever
- reviewer
- copier
- Note taker

Others

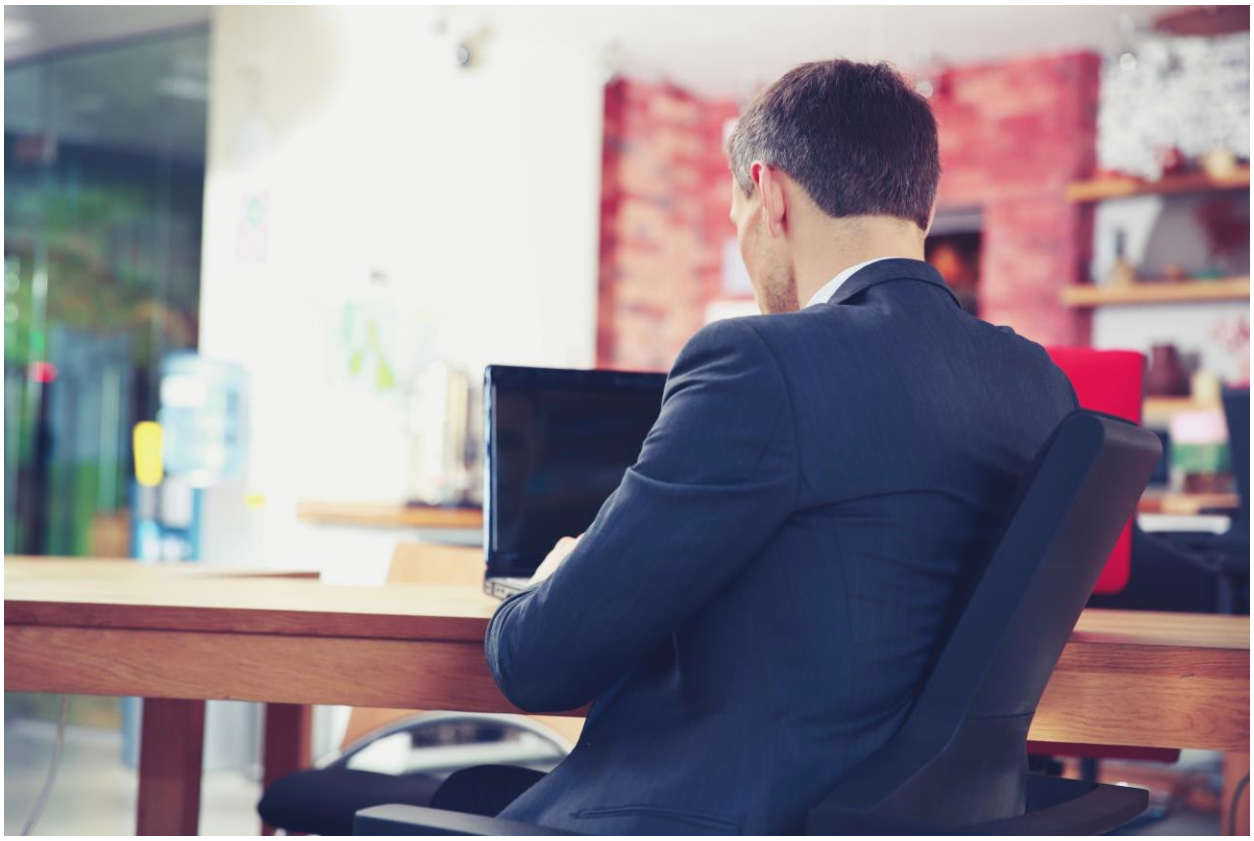
- Available to answer specific questions

"When I was trained as a host for FDA investigators, we always believed in a team approach," says Dr. Arbit. "I have found that this works out extremely well." In this approach one person is the Leader, and is responsible for the entire process. The Leader is the primary contact for the FDA investigator, and the primary responder for any questions.

The Leader must also act as the inspection coordinator. "You don't just leave the FDA to run the investigation," says Dr. Arbit. As inspection coordinator, the Leader must exercise control over the process, keeping everything organized and flowing. The Leader must also take notes. "Make sure you write down everything that takes place, the questions that are asked, the answers that are given," advises Dr. Arbit. "One of the things that you want to happen is for the investigator to leave sooner rather than later," says Dr. Arbit.

Of course, the Leader must be well-informed. "The Leader should be somebody who is well versed with the protocol and the research that's being done," says Dr. Arbit. The Leader must be free to devote full attention to dealing directly with the FDA inspector. That can be challenging.

"If the FDA wants copies of documents, you want to make sure you retain copies of the same documents. That's a lot to do." Dr. Arbit offers this example: "If the FDA inspector were to say, ‘I want to see all your case report forms,' your response might be, ‘We have 100 patients in this study and each case report form is three volumes. We can't possibly bring out that many books.



Could you tell us which patient reports you'd like to see? Do you want to see the first; do you want to see the last; do you want to see the ones in the middle. Do you want to see every tenth one?'"

The idea is to let the investigator determine which documents he/she wants to see. That's where the Runner comes in. The Runner is sent to retrieve the requested documents, one at a time, reviewing the documents in the process. "The Runner should be looking for problems," says Dr. Arbit. "Perhaps signatures are missing, and maybe the informed consent isn't in there." It is the Runner's responsibility to retrieve documents and make copies, freeing the Leader to remain with the FDA inspector.

Any errors in records identified by the Runner must be brought to the Leader's attention so the issues can be resolved. For instance, the Leader can explain to the inspector why a particular document is missing. "Maybe it's being circulated for approval or something of that nature," says Dr. Arbit. The Runner should also be responsible for making any photocopies the FDA inspector requires. "You don't want the FDA investigator to be standing at a copy machine, making copies while there are people idly standing around talking."

It's important to control the environment. "For example," says Dr. Arbit, "you may have two research coordinators talking about a totally different study, and one says, ‘Wow, did you see the rash on that patient? That was the brightest red I've ever seen.' I can almost guarantee you that the FDA investigator is now going to expand the investigation to follow-up on that comment."

What the FDA Inspector Wants

During the inspection, the FDA agent will be looking for different information from different stakeholders. From an investigator, the FDA wants the authority to conduct a study. The agent will also want to examine the protocols, subject records, informed consents, and IRB communication. In addition, the agent will ask about sponsor compliance, record retention, and electronic records.

The information required from the sponsor will be a bit different. “If you are the sponsor, either sponsor by the fact that you are industry or if you are the sponsor by the fact that you are a sponsor investigator, they're going to ask some additional questions," says Dr. Arbit. These questions will focus on the organization, on the selection and monitoring of clinical investigators, on adverse event reporting, data collection and handling, and on data tabulations, record retention, and test article accountabilities.

In addition, the FDA will want to know the source of the study subjects. Do the subjects meet inclusion/exclusion criteria? Are you following the protocol? Have you obtained informed consent? Have all the lab tests been done per the protocol? Do the tests results agree with the trial data? The inspector will ask about concomitant therapy, about reporting of adverse events, and about trace and disposition of test articles. "You can see that some of these requirements are repeated whether you're an investigator or you're a sponsor," says Dr. Arbit. "They just continue to come up."

The FDA will also want to see a list of documentation. They will want to see the current protocol, and may ask to see all iterations of the protocol and any amendments. They will want to see

informed consent documents, and may want to see any iterations or changes in those documents. They will also ask to see the approvals for each change in the protocol and informed consent documents.

Also on the FDA's list of required documents:

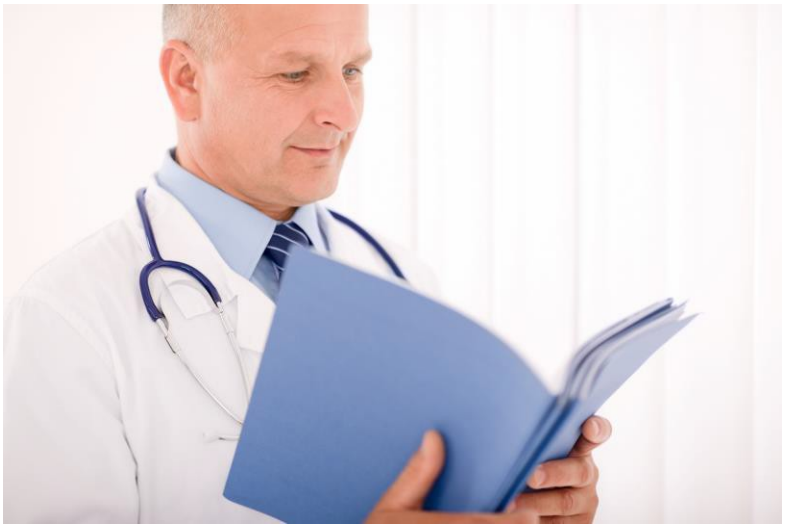
- IRB approvals and amendments
- CVs of primary personnel
- Publications from the study
- Other clinical trials
- Patient charts and lab reports
- Sponsor and IRB correspondence
- Monitor visit log
- Patient recruitment ads and IRB approvals
- List of labs and pharmacies used in the study

The FDA inspector will also ask to see information about who performed various aspects of the study protocol, and about whether the IRB approved the protocol and the informed consent form, whether the staff adhered to the protocol, and whether the informed consent documents were signed, and by whom. FDA questions will also focus on the authority to conduct study data, how is it obtained, where is it recorded, any accountability of the investigational product.

The inspector will want to know:

- Whether the authority to conduct aspects of the study was delegated, and if so, how the conduct of the study was supervised by the clinical investigator
- Whether specific aspects of the investigation were performed
- How the study data was obtained and where the study data was recorded
- Who is accountable for the investigational product, including shipping records and disposition of unused investigational product.
- The FDA agent will also seek to identify any conflict of interest by determining whether the clinical investigator disclosed information regarding his/her financial interests to the sponsor, and/or any interests of any sub-investigators, spouses, or dependant children.

The FDA will also want to look at the monitor's communications with the clinical investigators to determine whether they have been doing their jobs appropriately. The monitor's evaluations of the progress of the investigation are also subject to FDA review, as are any corrective actions in response to previous FDA inspections, and any regulatory correspondence and sponsor/monitor correspondence.



The inspection will also include an audit of study data, comparing data filed with the agency or sponsor with records related to the clinical investigation. These records may include case report forms and supporting source documentation, including signed and dated consent forms and medical records, physician progress notes, the subject's hospital chart, and nurses notes. "The records may be in hard copy, or they may be in electronic format," says Dr. Arbit. "If they're in electronic format you need to be sure that your institution is in compliance with 21 CFR, part 11 on electronic documentation."

Finally, during the inspection the FDA agent will want to examine the subjects' medical records that are part of the clinical investigation and predate the study in order to verify whether the condition under study was diagnosed, whether the study eligibility criteria were met, and whether the subject received any medication prohibited by the protocol. "Keep in mind that the patient's name is there," says Dr. Arbit. "But the FDA is authorized to see those patient names."

After the Inspection

At this point the FDA may have been at your site for a day, three days, or two weeks. "It all depends on what they're looking for and what happens during the inspection," says Dr. Arbit. "At the end, they're going to issue a Form 483, the notice of observations. At that time the FDA will also conduct an exit interview. They'll review and discuss the findings and observations, " says Dr Arbit. "Once that's done, FDA takes all this information back to the office to determine what next steps should apply in this ongoing investigation." These next steps may include:

- Barring data from being used to support the study
- Sending a warning letter

- Conduction a sponsor inspection
- Disqualifying the investigator
- Imposing a consent agreement
- Seizure of test articles
- Injunctions and prosecutions

What happens afterwards? "The clinical investigator may respond to the 483 observations orally during the exit interview," says Dr. Arbit. "This is a perfect time to discuss these observations with the investigator to assure that there wasn't some misunderstanding. Maybe some things have already been corrected that you can bring to the investigator's attention." There is no guarantee that the FDA investigator will alter the 483 observations. "But at least they can mark in their notes what actions have already been taken." Dr. Arbit says.

Once the review is completed the appropriate FDA Center sends one of the following types of letters to the clinical investigator.

Types of Letters

- **Informational or Untitled Letter** - Identifies deviations from statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. Such letters may request a written response from the clinical investigator.
- **Warning Letter** - Identifies serious deviations from applicable statutes and regulations. Warning Letters are issued for violations of regulatory significance, including those that may lead to enforcement action if not promptly and adequately corrected. Warning Letters are issued to achieve voluntary compliance, and include a request for correction and a written response to the agency.
- ***Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)*** - This is a process to disqualify the clinical investigator from receiving new investigational drugs or biologics, or investigational devices if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements, or has deliberately submitted false information to the sponsor of FDA in any required report.

"Keep in mind," Dr Arbit advises, "that they can only cite you on violations or deviations from the law and regulations. They cannot cite you for not following a guidance document."

Copies of any letters issued to you by the FDA are sent to the study sponsor (if you are an investigator under a commercial application), and to the interviewing IRB, so that everyone is aware of the situation. "They may also send a copy to the FDA division that may be reviewing

the marketing application," Dr. Arbit says. "If the data is not reliable, they may disallow the inclusion of that data in the marketing application."

All warning letters, disqualification proceedings, and other information about the clinical investigators who have been disqualified or restricted are posted on the FDA website. "It is your name, your facility, all the observations," says Dr. Arbit. "Unfortunately, the one thing that the FDA doesn't post is your response."

The 483 Response

While there is no regulatory requirement to respond to Form FDA 483, "it is in your best interest to respond in writing," says Dr. Arbit. "The FDA highly encourages this. I highly encourage this."

Why do something that is not a requirement? "It may mitigate further FDA compliance action, and that would be a nice thing," Dr. Arbit says. "It demonstrates to the FDA an understanding and acknowledgement of the observations. It demonstrates to the FDA a commitment to correct and voluntarily comply. Perhaps, most importantly, it establishes credibility with the FDA."

Elements of an Effective Response

The following list includes elements that will help to make your 483 response a strong one that supports your position.

1) Include a commitment statement from senior leadership
2) Address each observation separately
3) Note whether you agree or disagree with the observation
4) Describe corrective actions already taken, and any planned actions
5) Provide a method of verification and/or monitoring for corrections
6) Consider submitting documentation of corrections where reasonable and feasible
7) Be timely

"The first thing that you want to include is a statement or commitment letter from senior leadership," says Dr. Arbit. "Perhaps, the dean of the medical school, the vice president of the University, whatever it may be." The letter should make a strong statement about their compliance with FDA regulations.

"When you're writing your response address each observation separately," Dr. Arbit says." Don't write a narrative." State the observation, then follow with your response. Repeat that process for each observation. Note whether you agree or disagree with the observation. "Certainly, if you disagree, the FDA needs to know that, and you need to state why you disagree with the observation." Describe any corrective action you have taken or have planned. "Tell the FDA what your plan of action is," says Dr. Arbit. "Provide timeframes for those corrections."

When reasonable and feasible, you can increase the value of your 483 response by submitting documentation of any corrections. "The FDA can come back in to verify that you have in fact made those corrections," says Dr. Arbit. "If you can start a dialogue with the FDA and keep them informed step by step, you're increasing your integrity with the agency."

Finally, respond in a timely manner. "What's important here is that this response gets to your district office before the district office sends all that documentation down to Washington," advises Dr. Arbit. "This will be one of those pieces of information that will be used to determine what next steps the FDA should take."

The Purpose of Sanctions

Sanctions protect the integrity and quality of the development and approval process, and ensure that the rights and welfare research subjects are adequately safeguarded. "You will hear these same words used repeatedly in many of the FDA documents," says Dr. Arbit.

Warning Letters: Examples

FDA Warning Letters are form letters (see the example, below). "Each starts off by explaining why they have the inspection," says Dr. Arbit. "They talk about the bioresearch monitoring program. They talk about your responsibilities to adhere to the regulations, and it tells you that you have 15 days to respond to the warning letter. " Warning letters also present descriptions of the observations, citations of violations, and include examples of each observation.

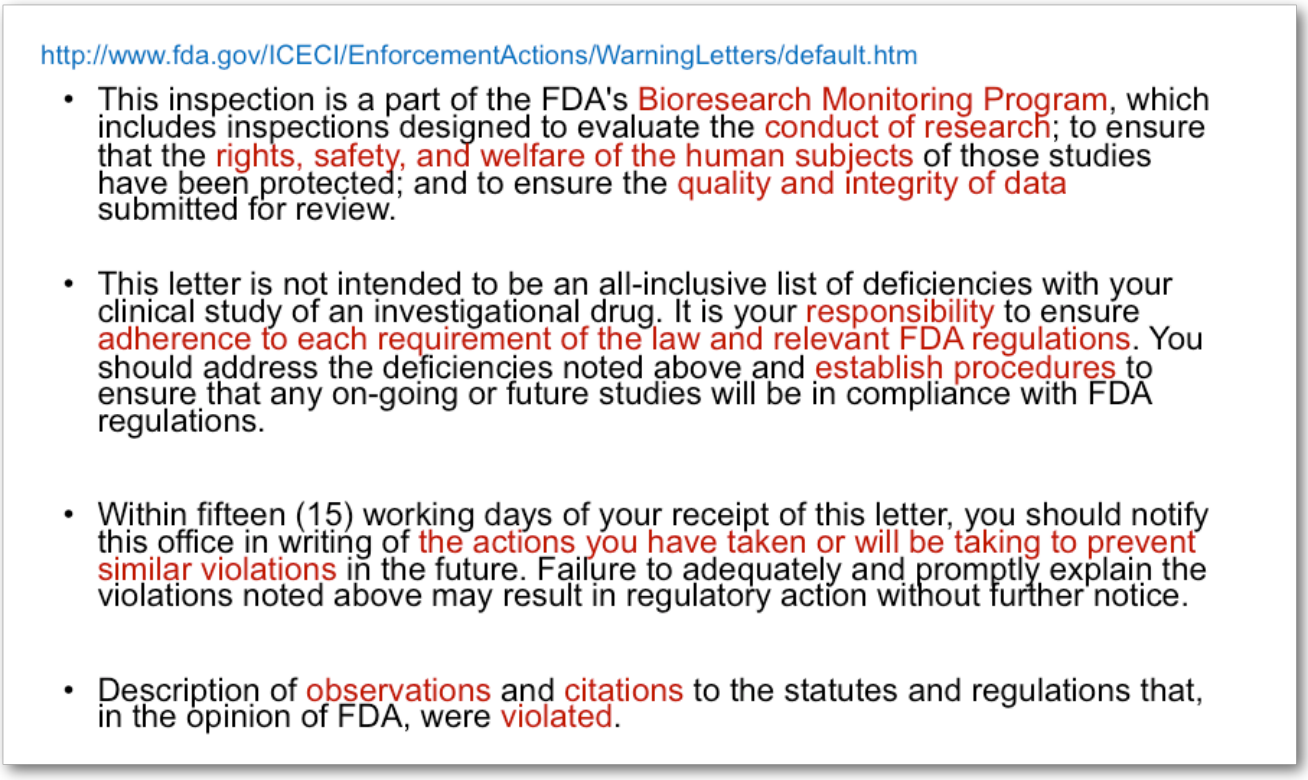


Figure 3: Warning Letter - General Text

Let's look as some examples of actual FDA warning letters. In the example below you will see the name of a physician and the institution. "That's not there to embarrass anybody," says Dr. Arbit. "That's there simply because the FDA has made that information public."

Alkis Togias, M.D.
Johns Hopkins Asthma & Allergy Center
3/31/03

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/warninglettersandnoticeofviolationletterstopharmaceuticalcompanies/ucm168924.pdf

FDA conducted an investigation into the death of a healthy volunteer who had received the drug, hexamethonium bromide, in the study, "Mechanisms of Deep Inspiration-Induced Airway Relaxation," in which you participated as a sponsor and an investigator.

Based on our evaluation of the inspectional findings, your written response to the Form FDA 483 and an informal meeting with FDA, CDER concludes that you violated the Federal Food, Drug, and Cosmetic Act (the Act) and FDA regulations governing the use of investigational new drugs by initiating a clinical investigation without submitting an IND. CDER also concludes that you failed to meet the obligations of a sponsor and an investigator under applicable regulations.

Sponsor Violations:

1. Caused the introduction or delivery of an unapproved new drug in interstate commerce.
2. Failed to submit an IND.
3. Failed to maintain an effective IND. Failed to submit supporting data and a study protocol.

Investigator Violations:

4. Failed to know and comply with applicable FDA regulations.
5. Failed to conduct the investigation in accordance with the protocol.
6. Failed to obtain proper informed consent.
7. Failed to maintain adequate and accurate records.

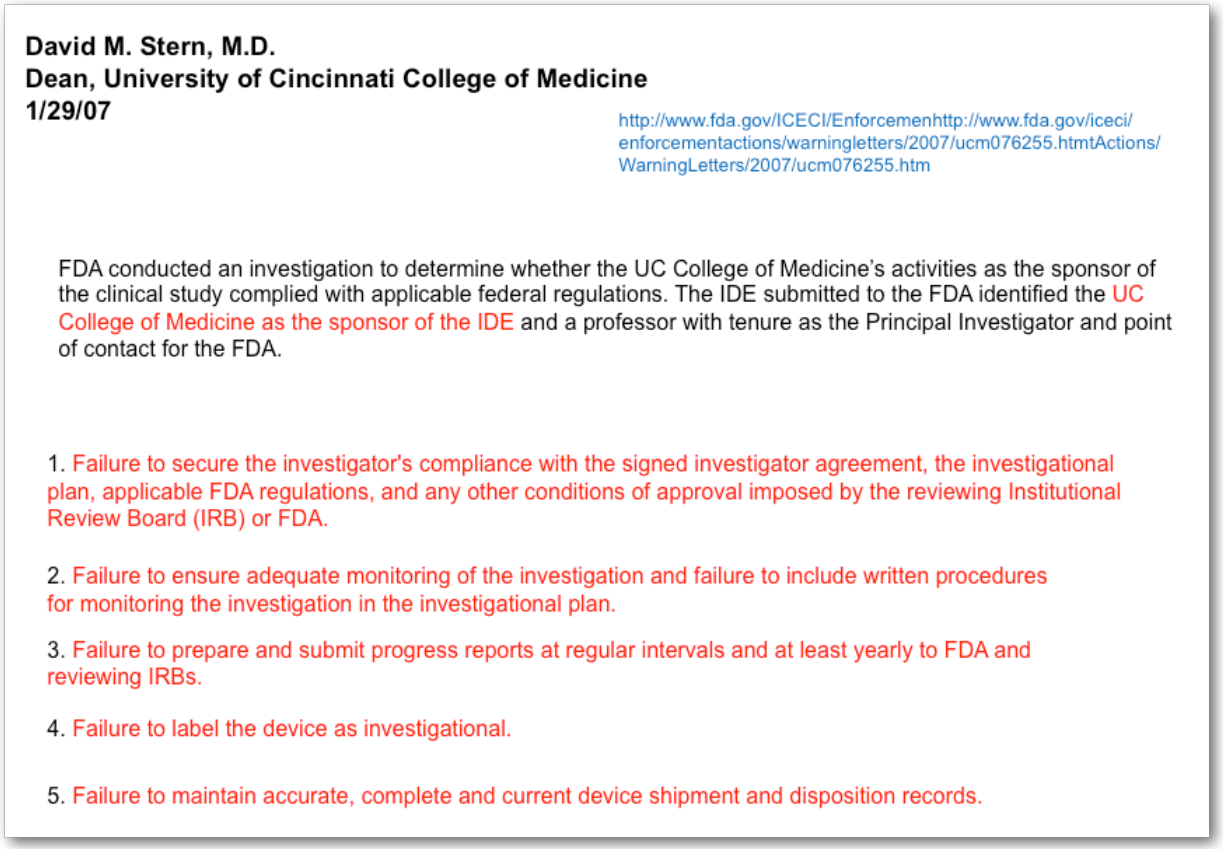
Figure 4: Warning Letter - Example 1

While this letter is thirteen years old, Dr. Arbit feels it is a particularly poignant example. In this case an experienced investigator administered his investigational drug to a healthy volunteer, who happened to be a member of his research staff. Sadly, this otherwise healthy young lady died. "The FDA came in, of course, did an inspection, and among other things they noted that he had failed to submit an IND. He also failed to knowingly comply with applicable FDA regulations, which of course follows if you don't file the IND." The investigator as not in compliance with any of the other obligations under an IND.

Because of these violations by a single individual, research at the university was shut down for several months until the situation could be evaluated and corrected. The consequences to the university were that research was basically shut down for several months until things could be evaluated and corrected.

In the example below, a faculty member at a College of Medicine thought he was doing the right thing. "He filed an IDE to do an investigational device study, and he listed the College of Medicine as the IDE sponsor. So far, so good," says Dr. Arbit. "Except he never bothered to tell

anybody in the College of Medicine that they were the sponsor." The faculty member also neglected to find out who would be responsible for assuring that the college was meeting its sponsor obligations."



David M. Stern, M.D.
Dean, University of Cincinnati College of Medicine
1/29/07

http://www.fda.gov/ICECI/Enforcemenhttp://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076255.htmtActions/WarningLetters/2007/ucm076255.htm

FDA conducted an investigation to determine whether the UC College of Medicine's activities as the sponsor of the clinical study complied with applicable federal regulations. The IDE submitted to the FDA identified the UC College of Medicine as the sponsor of the IDE and a professor with tenure as the Principal Investigator and point of contact for the FDA.

1. Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA.

2. Failure to ensure adequate monitoring of the investigation and failure to include written procedures for monitoring the investigation in the investigational plan.

3. Failure to prepare and submit progress reports at regular intervals and at least yearly to FDA and reviewing IRBs.

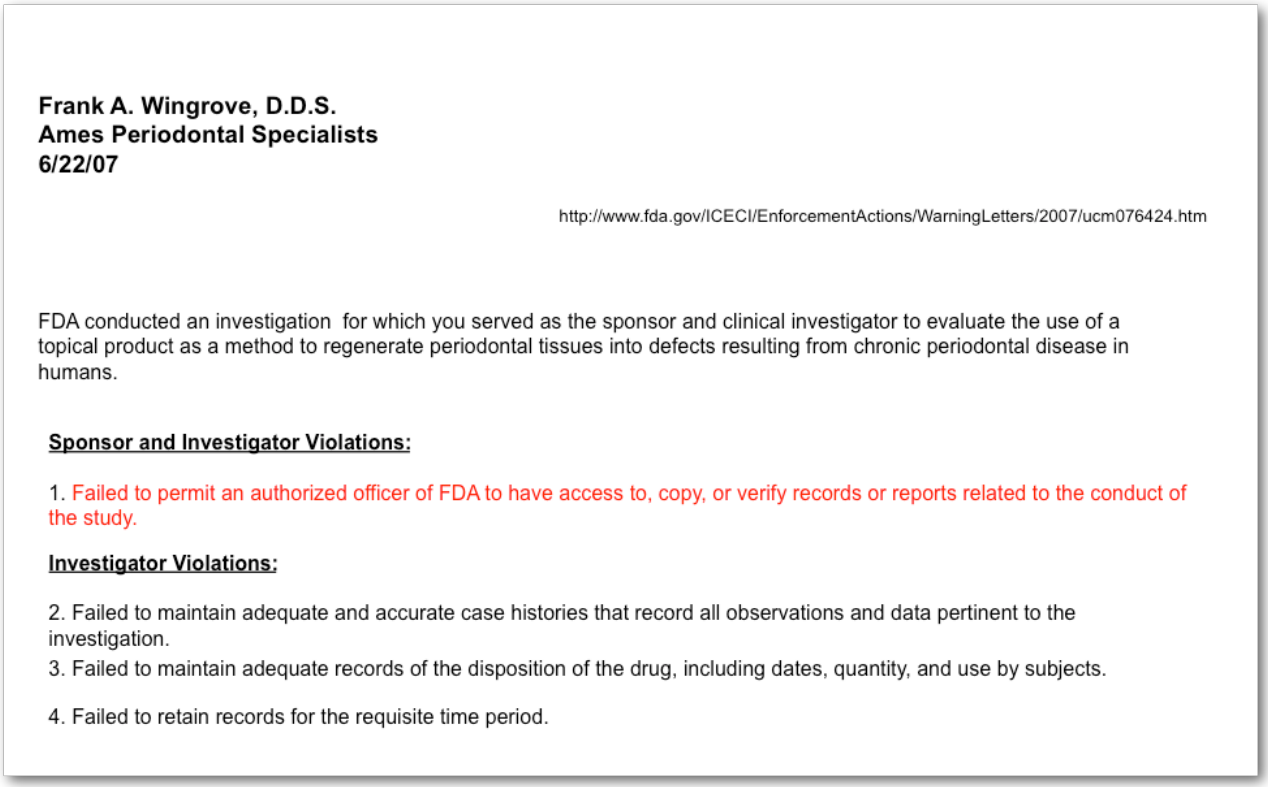
4. Failure to label the device as investigational.

5. Failure to maintain accurate, complete and current device shipment and disposition records.

Figure 5: Warning Letter - Example 2

"After two years of not submitting annual reports to the FDA, the FDA came in and performed an inspection," says Dr. Arbit. "They found that the College of Medicine had no clue that they were named a sponsor, nor what their responsibilities were." As a result, the sponsor was cited for several violations, including improper labeling of devices the failure to maintain records. "This type of warning letter could easily have been avoided," says Dr. Arbit.

In our final example, the sponsor investigator failed to permit inspection, and failed to give access to copy or verify records or reports. It turns out that the person responsible for the violation was the sponsor investigator's attorney. "He obviously didn't know very much about regulatory law," Dr. Arbit observes," and had suggested that perhaps the best thing to do would be to shred everything."



Frank A. Wingrove, D.D.S.
Ames Periodontal Specialists
6/22/07

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076424.htm

FDA conducted an investigation for which you served as the sponsor and clinical investigator to evaluate the use of a topical product as a method to regenerate periodontal tissues into defects resulting from chronic periodontal disease in humans.

Sponsor and Investigator Violations:

1. Failed to permit an authorized officer of FDA to have access to, copy, or verify records or reports related to the conduct of the study.

Investigator Violations:

2. Failed to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation.
3. Failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
4. Failed to retain records for the requisite time period.

Figure 6: Warning Letter - Example 3

Conclusion

This article has covered a lot of territory, and there is certainly a lot to digest. But Dr. Arbit stresses that there are a few key points you must remember.

- "A career as a clinical researcher is built on ethics and integrity," says Dr. Arbit. "Please don't allow your reputation to be compromised."
- Comply with the regulation. The consequences of failing to do so can be enormous. "There could be jail time," warns Dr. Arbit. "There could be fines and adverse press, all kinds of things that you really don't want."
- Dr. Arbit strongly recommends that you take advantage of the FDA's Guidance documents. "They express the FDA's current thinking," he says. "Even though they're not enforceable, it's a good idea to follow them."
- IND and IDE sponsors and investigators are under contract with the federal government. "If you look at many of the FDA documents, which have been signed by the investigator, state that a willfully false statement is a criminal offense," says Dr. Arbit. "If the FDA wishes to take action, it will be a felony."
- "We all know that if it's not written down it didn't happen," says Dr. Arbit. "The corollary is that if it didn't happen don't make it up. I think they call that fraud."

The most important thing to remember is that the FDA is your partner, "whether you like it or not," says Dr. Arbit. His recommendations can help to ensure a higher level of confidence and comfort in your next engagement with that partner.

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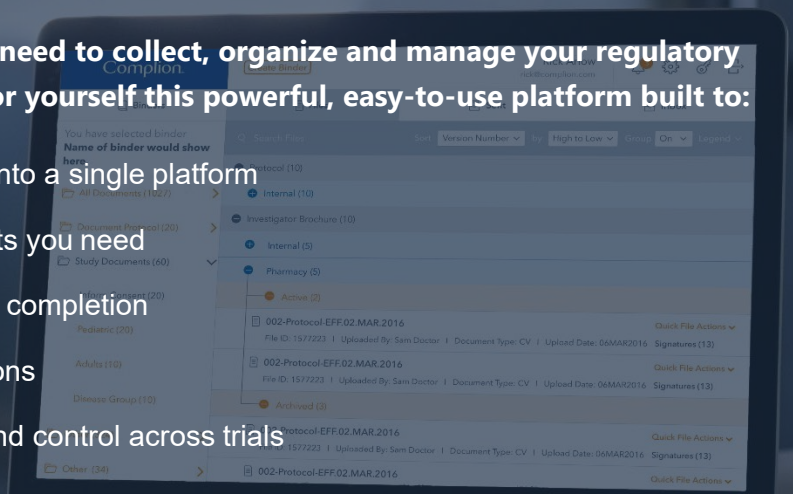

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