How to Prepare for an FDA Inspection

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Host

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Presenters

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Madeleine Williams, MA, CIP, is a Senior Director in Huron's Education practice. Maddie has over 15 years of research experience and her specific areas of experience include the management of engagements focused on clinical research compliance, research project management and Institutional Review Board (IRB) operations, structure and function. Maddie's focus is on helping organizations to improve their processes, enhance research compliance and improve efficiency

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Roberta Costello, MSN, RN has been working in clinical research in an academic hospital for about 20 years and is currently the Research Compliance Officer (RCO) for Albert Einstein Healthcare Network. In this role, Roberta serves as a support resource for researchers providing information related to compliance, auditing, and education. Roberta also has previous experience working as a research coordinator and project manager.

Learning Objectives

This webinar will cover the following key issues:

- What the FDA looks for during an audit
- Common findings of FDA inspections of the IRB and Investigators
- Examples of Establishment Inspection Reports (EIR), FDA Form 483s, and Warning Letters
- Example questions from/areas of focus for auditors specific to organization, responsibility, oversight, and compliance

Disclaimer

The information in this webinar is representative of the presenters' experience and does not necessarily represent the views of their employers or the FDA.

FDA Inspection Focus and Common Findings

FDA Inspection

Purpose is to:

- Determine that rights, safety, and welfare of study subjects are protected
- Determine that the quality and integrity of data are ensured
- Assess compliance with the FDA's regulations governing the conduct of clinical trials

FDA Inspection

- Specific to human drugs and biologics, animal drugs, medical devices, or foods
- May be announced or unannounced
  - Will keep time from initial contact to actual inspection as short as possible
  - Asking for a delay of more than a few days requires provision of significant justification

Triggers

- Routine / Complaint
- High / Fast enrolling site
- Pivotal trial / Test article is under scrutiny/of interest
- Safety reporting is outside of the existing profile
- PI with many studies / Study focus outside of PI area of expertise
- The Sponsor or another study site audited by FDA with findings

Most Common Findings

Clinical Investigator

- 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

IRB

- Inadequate initial and/or continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate meeting minutes
- Quorum issues
- Subpart D issues
- Inadequate communication with CI/ institution
- Specific to devices – lack of or incorrect SR/NSR determination

District Decisions for Inspections

No Action Indicated (NAI)	• No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further action).
Voluntary Action Indicated (VAI)	• Objectionable conditions were found and documented but the District and/or Center is not prepared to take or recommend any of the regulatory (advisory, administrative, or judicial) actions since the objectionable conditions do not meet the threshold for regulatory action. • A written response by the establishment may be an option, but is not necessary. Any corrective action is left to the establishment to take voluntarily. • A VAI classification should be made only if a FDA-483 has been issued.
Official Action Indicated (OAI)	• Objectionable conditions were found and one of the regulatory actions listed below should be recommended. • Typically, an OAI classification should be made only if a FDA-483 has been issued and the documented evidence supports the action recommended

2015 Biomedical Research Monitoring (BIMO)

Action	Clinical Investigator	Institutional Review Board
No Action Indicated NAI	64%	59%
Voluntary Action Indicated VAI	33%	37%
Official Action Indicated OAI	3%	4%

Investigator Warning Letter 9/2/14

At the conclusion of the inspection, Ms. Aspinwall presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your March 24, 2014, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated March 24, 2014, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

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

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocols **(b)(4)** and **(b)(4)** required that subjects self-record all pain assessments and have certain laboratory assessments completed. You failed to adhere to these requirements. Specifically:

a. Protocols **(b)(4)** and **(b)(4)** required that during the study period, subjects self-record all scores for pain-intensity and pain-relief assessments. However, site staff, rather than the subjects, recorded pain-intensity scores for the 20 subjects enrolled in Protocol **(b)(4)** and for the 3 subjects enrolled in Protocol **(b)(4)**. Of note, the primary efficacy endpoint for both studies was based on the pain-intensity scores that the subjects self-recorded.

IRB Warning Letter 11/10/15

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and the IRB's May 1, 2015, written response, we conclude that the IRB did not adhere to FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].

2. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].

3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].

Sponsor Warning Letter 6/16/15

At the conclusion of the inspection, Ms. Wright presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 10, 2014 written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your October 10, 2014 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

1. FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the protocols contained in the Investigational New Drug (IND) application. Our investigation found that you failed to ensure proper monitoring of Protocols **(b)(4)**, **(b)(4)**, and **(b)(4)**, and failed to ensure that clinical investigators conducted investigations in accordance with those three protocols. As a result of your inadequate monitoring, you did not identify, and did not correct in a timely manner, the clinical investigators' failure to report serious adverse events (SAEs) according to protocol-specified timeframes and failure to perform protocol-required laboratory tests. Examples include but are not limited to the following:

a. Your monitoring failed to identify and correct clinical investigators' failure to report SAEs within protocol-specified timeframes.

FDA Inspection Process

Areas of Focus

- Staff Responsibilities
  - Training
- Adherence
  - Protocol
  - Sponsor Guidelines
  - Institution Policy
- Study Records
  - consent document
- Drug / Device Accountability
- Reporting of Events
- IRB Communication
- Sponsor Communication
- Enrollment

Inspection Process

FDA Inspector	Site

➢ Receives assignment from FDA Office
➢ Contacts site and schedules visit
➢ Upon arrival
  ➢ Seeks most responsible person
  ➢ Shows credentials and issues Notice of Inspection (482)
➢ Conducts Inspection (2-10 days, can be longer)
  • Reviews Records
  • Interviews Staff
➢ Exit Interview
  • Summarizes findings
  • Responds to questions/clarifications
  • If findings are identified, issues Form 483
➢ Returns to FDA office and prepares report for FDA Office review
  • Report is reviewed and Inspection is classified
	➢ Receive Call from Inspector
	  ➢ Establish Purpose {random routine vs for-cause}
	  ➢ Inspector name, contact information
	  ➢ Anticipated visit length
	  ➢ What information is needed
	➢ Immediate notification of appropriate Institution Staff
	  ➢ Study team & involved departments
	  ➢ Sponsor
	  ➢ IRB
	  ➢ Institutional Official
	  ➢ Compliance
	➢ Get your site in order
	  ➢ Identify space for Inspector
	  ➢ Make sure key study staff are available
	  ➢ Gather and prepare requested materials
	  ➢ Identify point person

Prepare

- Protocol specifics
- Staff responsibilities
  - From the start of the study to current
- Review Investigator statement, 1572, Sponsor specific requirements
- Enrollment
- ‘Problems’ – be prepared to be asked about them
  - Lapse in approval
  - Implemented changes without IRB approval
  - Failure to report adverse events/serious adverse events according to reporting requirements (FDA, Sponsor, IRB)
  - Monitoring report findings

What will be requested?

Clinical Investigator

- Investigator Agreement
- CVs (PI, Sub-Investigators)
- Protocol and amendments
- Investigator Brochures
- IRB documents
- Sponsor monitoring visit records
- Correspondence w/ Sponsor, IRB
- Accountability records
- Subject files

IRB

- Records of IRB Membership
- IRB Policies and guidelines
- Minutes of IRB meetings
- Documents related to studies received for review by the IRB
- Documents related to studies sent by the IRB to the clinical investigator
- Any other materials related to study review

What happens when the inspection concludes?

On-Site	Exit Interview to summarize findings and if deficiencies have been found will issue a Form 483
Off-Site	The Inspector will prepare a written Establishment Inspection Report (EIR) • This, along with the form 483, copies of any materials collected during the inspection and any IRB response are for forwarded to the appropriate FDA center for further consideration
	After the above review, one of the following letters will typically be generated: 1. A letter that generally states that the FDA observed no significant deviations from the regulations. {This letter is not always sent} 2. An informational or untitled letter that identifies deviations from statutes and regulations for which voluntary corrective action is sufficient. Some will request a response be provided 3. A Warning Letter that identifies serious deviations from applicable statues and regulations. Generally requests prompt correction and a formal written response to the Agency

Example EIR

Summary of Findings

This inspection of a prospective manufacturer of was conducted as a follow-up to an earlier FDA inspection of 7/97. The finished produc

This firm will synthesize and supply th During the 7/97 inspection, several inspectional observations were noted and discussed with the firm. Immediate corrections were promised by the firm and the purpose of this follow-up was to determine if suitable corrective actions have indeed been enacted.

Credentials were shown and FDA482 issued to Mr.Herbert E. Paaren, Vice President of the corporation. Mr. Peter O. Johnson, President of the corporation is not present at the firm on a daily basis and was not present during this inspection. According, to Mr. Paaren, he himself is actually the person most responsible for day to day operations. He added that there have been no changes to the firm's ownership, responsible parties or corporate standing since the last inspection. Also present during this inspection were Christopher M. Henrich, QC, and Katherine J. Beardsley, Director of Regulatory Affairs. All three of these individuals answered questions and supplied document copies as requested.

This inspection was limited in scope and covered only the firm's correction of the previous FDA483 items.

#1. There is no documentation showing the procedures for the finishe product have been validated.

Example 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food and Drug Administration CBER / OCBQ 1401 Rockville Pike, Suite 200N HFM-604 Rockville, MD 20852 (301) 827-6191	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Edwin H. Wegman	PERIOD OF INSPECTION See below	C.F. NUMBER 2424009
TITLE OF INDIVIDUAL President and Chief Executive Officer	TYPE ESTABLISHMENT INSPECTED Biological Drug Manufacturer	
FIRM NAME Advance Biofactures Corporation	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 35 Wilbur Street	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Lynbrook, NY 11563	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Out-of-specification lots of Santyl ointment have been released after it was determined the method of calculating potency based on a [redacted] relationship of standard to sample was in error. The Agency had been advised in July 1999 that the results of the study, "Demonstration of the Equivalence of Laboratory-formulated Standard Collagenase Ointment and Actual Manufactured Standard Collagenase", approved 7/13-14/99 by Directors of Pharmaceutical Development and Quality Control, and the VP of Quality concluded that "there is no statistically significant difference in the results obtained from laboratory formulated and actual manufactured standard collagenase ointments". Later studies, conducted as early as January 2000, culminated with the reported conclusion in early June 2000 that historical potency data show that there is 70% recovery of the active in the ointment standard however, a 77% recovery in batches of final product ointment. Despite these findings, no modification to the existing method of determining potencies using the identified [redacted] conversion factor of [redacted] was made to SCP #102. Product continued to be released based on the earlier and erroneous [redacted] comparison of the results of these assays up to and including 7/25/00. From the beginning of June 2000 to July 25, 2000

FDA Inspection Example Questions

What is the FDA looking for?

- Understanding and Compliance:
  - Protocol
  - Regulations
  - Policy
- Organization and Control of Study Materials
  - Documentation: Complete, Accurate, and Legible
  - Test Article/ Device: Training and Accountability
- Oversight
  - Investigator
  - Sponsor
  - IRB

Resources

1. Bioresearch Monitoring Program (BIMO)
   -Explains inspection procedures (in great detail)

2. FDA Inspections of Clinical Investigators
   Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors

3. FDA Inspection Guideline
   -Explains parts of inspection
   -Provides Strategies for Audits
   -Provides an FDA Audit Checklist

BIMO Program Guidelines

1. If available at the clinical investigator's site, compare the Statement of Investigator Form FDA-1572 (human drugs and biologics) or the Investigator's Agreement (medical devices) with the information provided by the assigning Center.

2. **Obtain** a list of all studies performed by the clinical investigator. This list should include available information such as protocol number, protocol title, name of sponsor and study dates.

3. For the assigned study, **document** in the narrative of the EIR:

   a. The addresses of all locations at which study subjects were seen

   b. How the sponsor provided information to the clinical investigator about the test article, protocol, and the obligations of a clinical investigator (e.g., telephone, memo, meeting);

   c. The following dates:

   - IRB approvals (human studies) including initial review of the protocol, all amendments, the informed consent document and all revised informed consent documents;
   - For human studies, when the Form FDA 1572 or Investigator Agreement was signed by the clinical investigator (when available);
   - When the first subject was screened;
   - When the first subject signed the informed consent document;
   - First administration of the test article; and
   - Last follow-up for any study subject.

Protection, Quality of Data, Compliance

- Staff / IRB Member Responsibilities
  - Who did what
  - What responsibilities were delegated
- Study Conduct / Study Review
  - Where did the components of the study take place
  - Source document review
  - Eligibility Criteria review
- Study Oversight
  - How is test article accounted for
  - Monitor interaction with the investigator
  - Evidence of PI Oversight

Responding to Questions

- Professional, honest, factual, without emotion
- If you are not clear on the question, seek clarification BEFORE responding
- Only offer responses to questions that are within your scope of work
- Don’t reference a different study during a response
- Once you’ve offered a response, resist the urge to add more information or fill the silence
- It’s okay to say you do not know the answer

Questions about Responsibility

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Study Team	IRB
➢ Who ➢ Delegates study activity? ➢ How do you verify this? ➢ Determines delegated activities carried out by adequately qualified staff? ➢ Is there WRITTEN verification? ➢ Study specific training? ➢ Human research protection? ➢ Good Clinical Practice? ➢ Current licensure? ➢ Completes specific aspects of a study? ➢ Reviews/confirms inclusion/exclusion criteria? ➢ Introduces the study to potential subject? Obtains consent? ➢ Collects data? ➢ Reviews adverse events? ➢ Submits to the IRB?	➢ Who ➢ Is the Institutional Official for the IRB? ➢ Makes up the IRB committee? ➢ Appoints IRB members? ➢ Is able to complete review of materials submitted to the IRB? ➢ Determines the level of review required? ➢ Determines what member is assigned to complete a given study review? ➢ Makes determinations related to ➢ Approval /Disapproval? ➢ Level of Risk? ➢ Significant risk/Non-significant device? ➢ Frequency of review?

Questions about Data

Study Team	IRB

➢ Who has access to the study information?
➢ Where are study files maintained?
➢ Is there evidence that necessary approvals have been obtained?
➢ Who is responsible for the study test article/device?
➢ Are there accountability logs? Are they up-to-date?
➢ Are sponsor monitoring visits occurring as defined in the protocol?
➢ Are study files up-to-date?
➢ How are corrections made?
	➢ What are the criteria for approval?
	➢ How are qualifications of study team determined and evaluated?
	➢ Are reviews of on-going research conducted?
	  ➢ How is study selection made?
	  ➢ Who conducts the reviews?
	  ➢ What is the frequency of this type of review?
	➢ Who has access to the IRB files?
	➢ Who maintains the IRB files?
	➢ Are IRB files reviewed/audited?
	  ➢ Who does this? How often?

General Questions

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PI	Study Team	Institutional Review Board
• What made the PI agree to conduct the study? • What activities are the PI responsible for? • What activities did the PI delegate? • How are the staff trained? • Who were the staff that had contact with subjects, consenting process, data collection? • How does the PI oversee the study? • How is the study progressing ? • Does the study have a DSMB? • Have there been any findings that warranted change to the protocol? • Any issues of non-compliance? • Who is on the 1572?	• What is your role on the study? • Who identifies potential subjects? • How are subjects recruited? Enrolled? • When is study activity initiated? • What IRB has study oversight? • Have there been any changes to the study since it started? • Have you been trained on this study? • Are there special reporting requirements for this study? • Where is the study device / test article stored? • What are the source documents for this study? • Where are study materials maintained? • Who completed case report forms?	• Describe the review process for new submissions, modifications, reports of new information, continuing review • How is the significant risk / non-significant risk determination documented? • How are reviews that include special populations reviewed? • How are HUD reviews conducted?

Questions about Consent

- Process + Document
  - Are all required elements included in the consent form?
  - Was the most currently approved version used?
  - Are needed signatures obtained?
  - Did the individuals DATE the document?
  - Is there documentation of:
    - the consent discussion?
    - research activity initiated after consent obtained?
    - copy of signed/dated consent given to subject?

FDA Inspection FAQs

- Can a site refuse an inspector any information?
- Does the FDA review closed studies?
- What is the responsibility of a site to the FDA for an error that occurred when staff other than the current staff were responsible for the study?
- Will the FDA ever question past audits (483s) to see if your past response has been implemented and followed in the study that they are auditing?
- Does the Inspector also look for compliance with local policy and procedure?
- If there are several study coordinators at multiple sites, what's the best way to prepare for an audit?
- Is it always necessary to respond to a 483? Especially when,
  - You don't feel the findings are critical
  - You don't agree with the findings
  - You don't feel 15 days is sufficient time to provide an adequate response

Take Away Thoughts

- Be routinely prepared, not urgently scrambling
  - Have a plan for when the Inspector comes
  - Meet with study staff regularly
  - Keep files organized
  - Do random audits of your materials

Take Away Thoughts

- Follow Institution policy for escorting Inspector every day
- All discussion is official
- Expect questions to come up more than once
- Try to anticipate questions

Take Away Thoughts

- Not expected to be perfect
- (Most) Findings can be addressed
- Inspectors are doing their job
  - They know what they are looking for
  - They know how to find the problems

Take Away Thoughts

- Know your institutions policies
- Know the IRB of record policies
- House study materials securely
- Have a point person present when interviews are conducted to take notes, collect any requested materials

Stay Calm
Listen
Keep Focused
Be Professional
Utilize Resources

References

BIMO Program

- http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm

FDA Tip Sheets and Guidance- Clinical Investigator

- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

FDA Tip Sheets and Guidance – IRB

- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126555.pdf

Self-Evaluation Checklist for IRBs

- http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118063.htm

Questions?

Thank You

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