USFDA CLINICAL INSPECTION: An Industry Experience

Tom Caglioti

Exec. Director – Cordis Performance Support

Cordis Corporation

Warren, New Jersey; USA

908 412 7264

AHWP –Asian Harmonization Working Party

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Who is FDA?

United States Food and Drug Administration

U.S. Food and Drug Administration

http://www.fda.gov/

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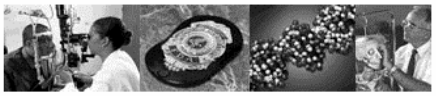
Products FDA Regulates

Food
Foodborne Illness, Nutrition, Dietary Supplements...

Drugs
Prescription, Over-the-Counter, Generic...

Medical Devices
Pacemakers, Contact



FDA NEWS

Avoid Raw Clams and Oysters from Pacific Northwest, FDA Warns

FDA Clarifies Information in JAMA Article on Defibrillator Recalls

Pharmacies Warned to Stop Mass-Producing Unapproved Inhalation Drugs

FDA Seeks Comments on New System for Identifying Medical Devices

FDA Forms Internal Nanotechnology Task Force

Recalls, Product Safety

Food Industry

- Register a Facility
- Prior Notice of Imports

Hot Topics

- West Nile Virus
- Hurricanes
- Flu Information
- FDA Centennial
- Losing Weight
- Buying Medicines Online
- Counterfeit Drugs
- Imported Drugs
- Counterterrorism
- Bioterrorism Act
- More Hot Topics...

FDA Activities

- About FDA

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FDA Role

- Oldest Consumer protection agency in the US (100 years)
- Areas of authority:
  - Foods; human and veterinary drugs; cosmetics; blood products; medical devices; radiological products; vaccines; human tissue.
  - Review of new product data and approval of marketing applications
  - Products made outside the US must meet FDA requirements

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How FDA Promotes Compliance

- US Congress establishes laws for consumer products
- FDA is authorized by Congress to issue regulations telling industry how the laws will be applied (what is expected)
- FDA inspects all areas being regulated to assess compliance with applicable laws
  - Food Drug And Cosmetic Act – 1938
- Industry is provided the regulations in the Code of Federal Regulations
  - Planned changes are communicated in the Federal Register

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Regulations Specific to Clinical Operations

- **Title 21, Chapter 1-** Food and Drug Administration, Department of Health and Human Services:
  - **Parts 11 - Electronic records; electronic signatures**
  - **Part 50 - Protection of Human Subjects 5/80**
  - **Part 54 - Financial Disclosure by Clinical Investigators - 2/99**
  - **Part 56 - Institutional Review Boards - 1/81**
  - **Part 312 - Investigational New Drug Application - 3/87**
  - **Part 314 - New Drug Application**
  - **Part 812 - Investigational Device Exemptions - 1/80**
  - **Part 814 – Premarket Approval of Medical Devices**

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FDA GUIDANCE DOCUMENTS

- Documents prepared by the Agency to describe “how to” comply with a regulation
- Issued where clarification of the regulation is required
- Variation in specified procedure is allowed, but must achieve same outcome

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GLOBAL CONSIDERATIONS - ICH

- Six parties
  - European Union (EU)
  - Japan Ministry of Health and Welfare (MWH)
  - US FDA
  - European Federation of Pharmaceutical Industries Association (EFPIA)
  - Japanese Pharmaceutical Manufactures Association (JPMA)
  - US Pharmaceutical Research Manufactures Association (PhRMA)
- Observers (World Health Organization (WHO), European Free Trade Area, Canada)
- IFPMA (International Federation of Pharmaceutical Manufacturers Association)

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FDA AUTHORITY OUTSIDE US

- If a clinical study is being conducted under a Investigational New Drug (IND) or a Investigational Device Exemption (IDE), then the FDA regulations will apply
  - Clinical sites can be inspected by FDA and held accountable for compliance
- FDA has agreements with local agencies to enforce regulatory actions if necessary
- FDA can refuse to allow the site's data to be considered in the Sponsor's application

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INSPECTION PROCESS

- Most likely to occur within 6 months of a regulatory submission
  - Average 3 clinical investigator sites per study
  - ~3-5 days in duration per site
- For US – usually receive short notice of inspection
  - International – Will notify well in advance to coordinate inspection / travel

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HOW YOU CAN PREPARE

- Ensure Sponsor is aware of the upcoming inspection
- Have all study documents available
- Have knowledgeable study staff available
- Have a work area ready for FDA with access to photocopy machine
- Organize correspondence with IEC/Sponsor
- Have Informed Consents ready for review
- Escort FDA at all times

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FDA PREPARATION

Prior to inspection, Field Investigators receive:

- total number of subjects entered into study
- total number of dropouts
- a list of other studies performed by the investigator and/or that sponsor is conducting
- a list of all AEs and deaths (with description and cause)
- any previous inspection history for the site and Principal Investigator

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FDA INSPECTION REFERENCES

www.fda.gov/ora/compliance_ref/bimo/default.htm :

- Compliance Program Guidance Manuals (CPGMs)
  - Written by FDA for their Investigators, describe **how to conduct the inspection**
  - CPGMs for IRB/IECs, Clinical Investigators, Sponsors, CROs, and Monitors
- CFR Sections:
  - 50 – Protection of Human Subjects
  - 54 – Financial Disclosure by Clinical Investigators
  - 56 – Institutional Review Boards
  - 11 – Electronic Records / Electronic Signatures

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WHAT WILL BE LOOKED AT?

- Authority and Administration
  - Who is responsible for what?
  - Who has been delegated which responsibilities?
  - Is everyone qualified to perform their assignments?
  - Is all of the above documented?
- Study Protocol
  - What version is being used?
  - Has everyone been trained in it?
  - What deviations /amendments / waivers are documented?
  - Necessary approvals in place?
- Laboratory Usage
  - Which labs are used?
  - Is the lab qualified for the tests they perform?
  - Does the lab Manager and staff have appropriate credentials?
  - What acceptance criteria is used for the tests they run?

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WHAT WILL BE LOOKED AT?

- Subjects' Records
  - How are records kept? (Electronic? Hard–copy?)
  - Do the subjects really exist?
  - Do source documents support Case Report Forms?
  - How many drop-outs and why?
  - Adverse Experiences fully documented, with follow up?
  - Medical Histories complete?
  - Were inclusion/exclusion criteria met?
- Informed Consent
  - Can copies of all consent forms be obtained?
  - Was the consent form being used approved by the IEC?
  - Were all subjects consented prior to any study-related procedures?
  - How were vulnerable subjects consented?
  - Was translation provided where needed?
  - Were there any "emergencies" where consent was not obtained prior to the procedure?

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WHAT WILL BE LOOKED AT?

- Independent Ethics Committee
  - Is there evidence of IEC approval before study start?
  - Are there records of safety reports to IEC?
  - Does investigator maitain copies of correspondence with IEC and IEC decisions?
- Sponsor communications
  - Is Sponsor notified of all AEs?
  - Documentation of protocol deviations or amendments needed?
  - Documentation of any study-related issues or concerns?
- Product accountability
  - Documentation of receipt of test article (quantity, lot #, date, etc.)
  - Accurate inventory records?
  - Appropriate storage conditions and security for test article?
  - Documentation of all inventory transactions and disposition?

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WHAT WILL BE LOOKED AT?

- Records keeping & retention
  - Are records readily available and legible?
  - Are signatures entered only by study personnel with proper authority?
  - Are corrections made properly ans with explanations where necessary?
  - Are records retained for 2 years after FDA is notified that the study is terminated?
- Electronic records & signatures
  - Have you identified which study records will be accessed via electronic systems?
  - Has everyone using the system been trained?
  - Is there a change control process in place for the system?
  - Is a back-up system established and qualified?
  - Are the electronic systems identified meeting Part 11 requirements? (audit trail; open/closed system controls, etc.)

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INSPECTION OUTCOME EXAMPLES

- At least two subjects who should have been excluded from the study because they exceeded the BMI criteria specified in the protocol were enrolled in the study..
- Numerous case report forms reviewed contained inaccuracies or were incomplete..
- Adverse Event reports were filed with the sponsor for subject X. However, there is no documentation that the IRB was notified of the adverse events..
- Informed Consent for three subjects could not be located

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INSPECTION OUTCOME EXAMPLES

- The device accountability records are incomplete, and several entries for shipment dates and patient identification numbers are missing for each study site. There are also no records to account for 6 devices sent from the manufacturer to the clinical investigator at one site

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INSPECTION OUTCOME EXAMPLES

General areas of citation:

- Shadow charts do not reflect hospital charts
- No evidence of adequate PI involvement
- Missing source documents
- Subjects not re-consented for significant protocol changes
- Protocol deviations not reported to IEC
- Informed Consents not signed appropriately
- Inclusion / exclusion acceptance criteria violations
- IEC/IRB oversight not adequate

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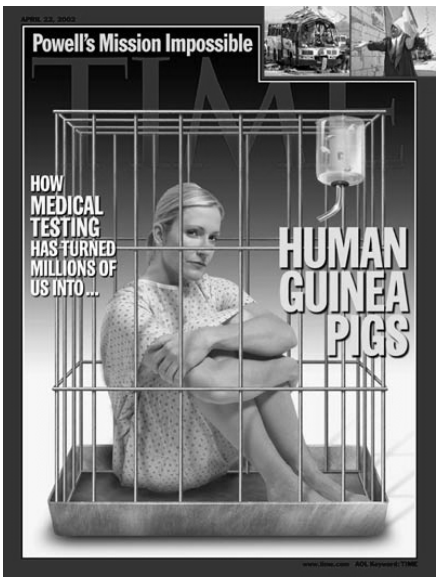
PUBLIC PERCEPTION..



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FDA REACTION..

- Sensitive to “Fraud and Abuse” activities
- If FDA has evidence that an investigator has repeated or deliberately failed to comply with GCP, or has submitted false data to FDA or sponsor:
  - Written notice will be sent to investigator with offer for investigator to explain
  - If explanation not accepted, opportunity for regulatory hearing
  - If judgment is against investigator, he/she and sponsor is notified that investigator is no longer entitled to receive investigational articles

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FRAUD

- Intentional, repeated non-compliance and negligence – *misconduct* - relative to GCPs and regulations, e.g.:
  - Deliberate protocol violations
  - Altered data
  - Omitted data
  - Manufactured data
  - Retrospective completion of CRF or source
  - Consent interviews by nonqualified site personnel
- Does not include errors due to accidental mistakes

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WHAT MAKES FDA SUSPICIOUS?

- Complaints about activities at the clinical site:
  - subjects
  - sponsor
  - employees or ex-employees
  - anonymous
- Subject injuries or fatalities
- Excessively high amount of subjects at the site

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WHAT MAKES FDA SUSPICIOUS?

- Data that is too good to be true
  - Absolute efficacy
  - Little or no toxicity
  - Few if any drop outs
  - Problem-free lab results on subjects
- Results of handwriting analysis
  - Same person has different handwriting
  - More than one person with same handwriting
  - Subject informed consent signatures signed by site personnel
  - PI signs for *everything*

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DOCUMENTATION ISSUES

(The Pathway to Problems)

- Can you provide the information readily?
- Notations out of chronological order
- Data "squeezed in" between lines
- Copies of charts, EKGs, lab reports, etc., where there should be originals
- Perfectly clean data
- "Patterns" of data
- Unusually high volume of data for the amount of staff at the site

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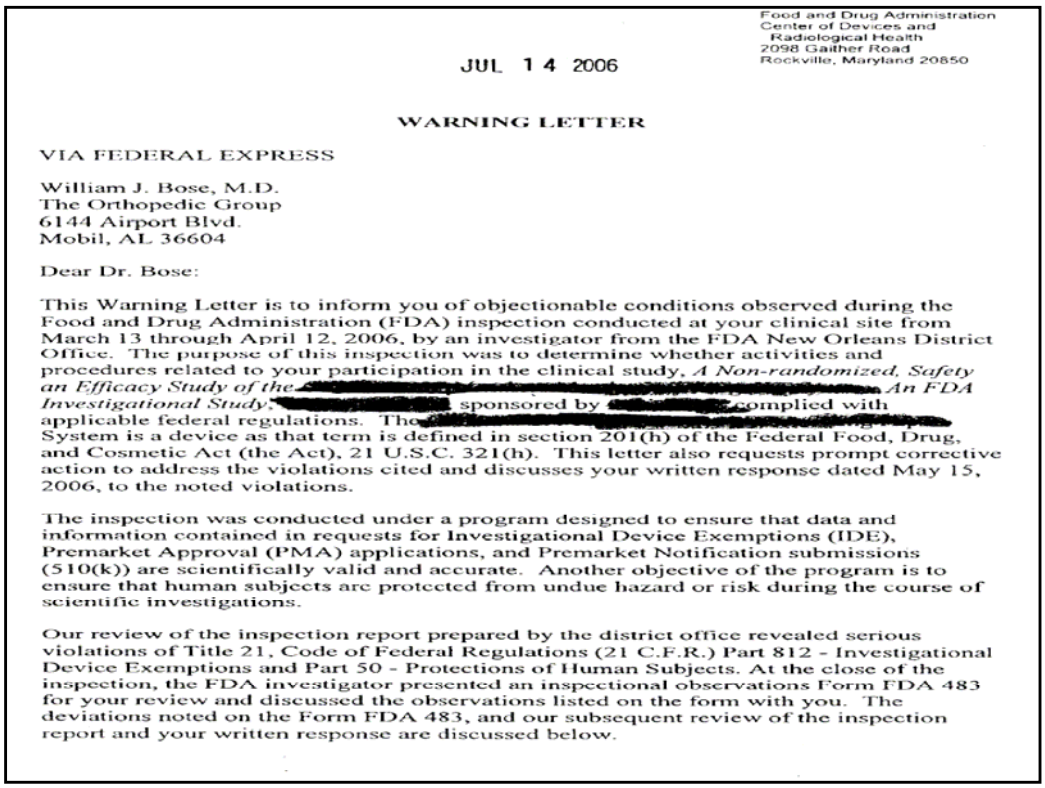

Food and Drug Administration
Center of Devices and
Radiological Health
2098 Gaither Road
Rockville, Maryland 20850

JUL 14 2006

WARNING LETTER

VIA FEDERAL EXPRESS

William J. Bose, M.D.
The Orthopedic Group
6144 Airport Blvd.
Mobil, AL 36604

Dear Dr. Bose:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from March 13 through April 12, 2006, by an investigator from the FDA New Orleans District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study, *A Non-randomized, Safety an Efficacy Study of the* [redacted] *An FDA Investigational Study*, [redacted] sponsored by [redacted] complied with applicable federal regulations. The [redacted] System is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response dated May 15, 2006, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.) Part 812 - Investigational Device Exemptions and Part 50 - Protections of Human Subjects. At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, and our subsequent review of the inspection report and your written response are discussed below.

In your response, you acknowledge that at the onset of the study you were unfamiliar with the requirements and complexity of documentation for an IDE clinical study and that your study coordinator was also inexperienced and not trained to these requirements. You acknowledge your role and responsibilities as a clinical investigator and state you will work diligently with the FDA, the reviewing IRBs, and the sponsor to ensure that all observations made by the FDA have been fully addressed and that all future activities comply with the applicable regulations. You have taken steps to correct some of the violations noted, however, your corrective action plan does not fully address all the noted violations. You and your coordinator may consider seeking training specific to medical device good clinical practice (GCP).

Failure to ensure an investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

1. You failed to maintain documentation of correspondence with the two reviewing local IRBs [redacted] for reporting of adverse events/complications in accordance with the investigational plan and IRB policy. Examples of this failure include, but are not limited to the following:

   A) Subject [redacted] was hospitalized for cellulitis. The subject received intravenous (IV) and oral (PO) antibiotics for three weeks in December 2003. There is no documentation that the IRB was informed of this event and hospitalization.

   B) Subject #[redacted] became pregnant during the study and could not have X-Rays performed in accordance with the investigational plan, however there is no documentation the pregnancy or deviation from the investigational plan was reported to the IRB.

   C) Subject #[redacted] developed an abscess around the implanted device that required removal of the device. There is no documentation that the IRB was informed of the event and that the investigational device was removed.

In your response, you acknowledge that documentation of correspondence with the IRBs was not accurately maintained. You state that in the future all IRB correspondence, submission, approvals, and reviews will be maintained in the regulatory binder. Doing this should assist you in the maintenance of correspondence documentation. Your response is incomplete in that it did not address ensuring all correspondence/reporting is performed in accordance with the investigational plan, IRB policy, and Federal Regulations. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure correspondence with the IRB, the sponsor, and regulatory agencies is performed as required.

2. Subjects were enrolled that did not meet the eligibility criteria. Examples of this failure include but are not limited to the following:

   - Subject [redacted] and subject [redacted] have documented diagnoses of morbid obesity (according to the diagnoses listed in their medical history), however, morbid obesity is an exclusion criteria as dictated by study protocol.

Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50. [21 CFR 812.100 and 21 CFR 50.27]

An investigator is responsible for ensuring that the Institutional Review Board (IRB) approved version of the informed consent document is obtained from each subject participating in the investigation prior to performance of any study-related procedures. You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- Subject #[redacted] had the investigational device implanted on January 12, 2004, however, the consent was not signed until February 9, 2004.

In your response, you state your research team was unable to locate the original consent document, but subject [redacted] was consented. You acknowledge that your coordinator "backdated" the consent document for subject [redacted]. You are adding a note to the file to clarify this issue.

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Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]

You failed to maintain accurate, complete, and current records of each subject's case history and exposure to the device, as required by 21 CFR 812.140(a)(3) and the study protocol. Examples of this failure include, but are not limited to the following:

1. Protocol inclusion #6 requires subjects to have a pre-operative Harris Hip Score (HHS) of less than 70 . Harris Hip Scores were not documented in 21 of 21 subjects' charts inspected by the FDA investigator.

In your response, you note you did not document the actual HHS for subjects prior to enrollment, but you evaluated each patient preoperatively and only patients who had a HHS of less than 70 were enrolled. You acknowledge that documentation of the inclusion-exclusion criteria should have been completed in the patient's medical history.

2. Discrepancies were observed between source records and case report form (CRF) entries. Examples include:

   A) Subject [redacted] underwent right hip arthroscopy with resection of labral tear on January 6, 2004, however, this prior surgery was not documented on the May 17, 2004, pre operative CRF. The check box on the CRF asking if the subject has had prior surgery in the past 12 months was checked "no".

   B) Subject's [redacted] and [redacted] have discrepancies in the documentation of the size of the implanted cup. The sizes noted on the CRFs and on the operative reports differ.

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Failure to maintain records of device receipt, use, and disposition. [21 CFR 812.140(a)(2)]

You failed to maintain device accountability records. Investigators are responsible for maintaining records of receipt, use, or disposition of a device that relate to the following: type and quantity of the device; dates of its receipt; batch number or code mark; names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

- There were no device accountability records to show receipt, use/implantation, and disposition/return to the sponsor of investigational devices.

You noted in your discussion with the FDA investigator the sales representative brought the devices directly to the operating room prior to their implantation. It is an investigator's responsibility to maintain records of an investigational device receipt, use, and disposition.

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The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

During the inspection you discussed with the FDA investigator that you believe some of the observations on the Form FDA 483 were the responsibility of the sponsor, and that you trusted the sponsor was following all regulations. The regulations in 21 CFR Part 812 describe sponsor responsibilities for the conduct of investigational device studies as well as those of investigators. The regulations in 21 CFR Part 50 describe responsibilities of the investigator and IRB in the informed consent process and IRB responsibilities are spelled out in 21 CFR Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 C.F.R. 812.119.

MAXIMIZE YOUR CHANCES OF A SUCCESSFUL INSPECTION

- Develop and follow SOPs
- Understand the protocol and get involved
- Train and educate staff
- Maintain adequate & accurate records
- Document and fully explain any non-compliance
- Maintain open dialogue with staff and monitors to resolves issues
- Check the FDA website for examples and assess your vulnerability

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