FLAWLESS FDA INSPECTION HANDLING AND RESPONSE

PRACTICAL EXERCISES FOR SUCCESS

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Helpful Reference Materials, Templates, Checklists, and So On

All attendees should have the following materials to help you quickly and easily implement the advice in this workshop:

Slide handouts (3 slides per page)

Checklists, template and sample SOP

- Checklist: Site Inspection Proof Binder
- Checklist: FDA Inspection Handling
- Checklist: Pre-Inspection Activities
- Checklist: Post-Inspection Response
- Template: Inspection Observation-Closure Matrix
- Sample SOP: Handling Regulatory Agency Inspections

FDA inspectional policies and guidance documents

- 6 different FDA forms (463a, 482, 483, etc.)
- FDA IOM Chapter 5 – Establishment Inspections
- FDA Inspection Manual for Devices, 2011-2015
- FDA Quality System Inspection Technique (QSIT), 1999
- 2 FDA Inspection Compliance Program Guides (pre-approval and post-approval)
- ORA FDASIA 707 Inspection Guidance (circumstances that delay, deny, etc.)

Internationally harmonized inspectional guidances also used by FDA investigators

- GHTF/IMDRF Auditing Manufacturer Control of Suppliers
- GHTF/IMDRF Auditing Quality Systems Used at Multiple Sites
- PIC/S Aide Memoire on Inspecting GMP Production During Clinical Trials
- PIC/S Inspecting GMPs for APIs
- PIC/S Inspecting GMPs for Medicinal Products
- PIC/S Inspection Considerations for Computerized Systems in GXP Environments

Bonus documents

- Article, “Rapid Deployment Tips to Prepare for a Sudden FDA Inspection” PDA Letter, September 2010
- and 6 more bonus documents….

Exercise #1: Inspecting a Company for Compliance

In this exercise, you play the part of a skeptical FDA investigator. Pretend that you are conducting an inspection of the company that you actually work for in the real-world.

Below is an entry that you found (as the FDA investigator) in the company's records of a complaint investigation:

> "No malfunction of the [manufacturing/lab/clinical] equipment was determined. Based on the provided information and investigation on site, this was caused by the machine operator who accidentally dropped the top part of the machine. No further investigation or corrective action is warranted."

1. List some questions that you might ask about this entry to determine if the company was trying to hide something.

2. As the FDA investigator, if you were trying to decide whether or not to cite the company for noncompliance (such as for having poor investigative techniques as part of their CAPA program, poor complaint investigations, etc.), what might the company be able to show you that would give you assurance that the firm was operating in a state-of-control and that the above entry was truly correct and all that's needed? Be creative and make up any necessary documents or facts.

Exercise #2: Understanding FDA-483 Observation Seriousness

You play the part of an FDA investigator writing up his/her Form FDA-483 set of observations.

Put in order the seriousness (e.g., presents the *most immediate* risk to public health) of each of the following observations. Each of these are real-world observations from companies over the past four years.

_____ There is a failure to manufacture products in a clean, sanitary manner. Specifically, sterile, released product is being packed for shipment by employees with bare hands into cardboard cartons.

_____ Equipment used in the manufacture of product is not adequately maintained. Personnel were observed using out of calibration scales to weigh incoming materials even though the SOP stated that personnel were not to use equipment that is out of calibration.

_____ Laboratory samples are not adequately controlled. Two of five standard storage (2-8C) refrigerator units containing product stability samples were broken and unable to maintain uniform temperatures.

_____ Failure to thoroughly review any unexplained discrepancy and failure of a product batch/lot. Specifically, employees were observed repeatedly testing and retesting product samples when QC tests were failed.

_____ Requirements that must be met by suppliers have not been adequately established. Your SOP […] states that ingredient and component makers "must implement sufficient controls to comply with specifications." However, no controls for incoming materials have been established by your firm nor have you qualified your suppliers or any controls they may have.

Exercise #3: Initial FDA Inspection Handling

Read the example internal email below and answer the following questions.

> From: Sara Smith, Director of Quality
> To: All Employees
> CC: ssmith21@gmail.com
> Subject: FDA is HERE!!!!
>
> Two FDA inspectors showed up a couple of minutes ago at the front desk. I'm having them cool their heels while I write this heads-up to everyone.
>
> As of yesterday, nobody had corrected all my internal audit findings from last month, so as of right now, everyone is to stop all other activities and FIX those problems! And Craig, grab the janitor and you two empty all the trashcans everywhere.
>
> (I can't believe you people have let all these noncompliances go for a month and no one has taken any corrective actions.) We'll be lucky if we just get a warning letter.
>
> I really worry that a failed inspection will make us look bad in the press. See what happens when you guys don't take quality seriously?

Questions to answer:

1. Why did the Director of Quality write this email and send it out to everyone at the company?

2. What are two (2) problems with this email?

3. List some concepts you would include in a revised email alert to your company about a surprise FDA inspection at your facility.

Exercise #4: Completing an Observation-Closure Matrix

Your firm has just had an FDA inspection and is expecting to have the closeout meeting tomorrow morning. Using the below Inspection Observation-Closure Matrix, review the following 4 anticipated observations that the investigator has already suggested you are likely to receive on the Form FDA-483 tomorrow.

Fill out the matrix with the appropriate titles of people in your company who would address each observation, along with the recommended set(s) of proof you would provide to FDA in the morning closeout meeting to prove that the gap has been closed.

Your goal is to try to avoid getting all four FDA-483s (e.g., you want to be able to show the investigator that you have closed – and gone at least one step beyond – as many of the four likely observations as possible). Be creative in your responses and proof.

Inspectional Observation	Owner/Accountable	Status	Proof (records)

Anticipated observations:

1. cGMP training is not consistently conducted to assure that employees are familiar with cGMP requirements.

2. Adequate laboratory facilities are not maintained. During our inspection of the QC laboratory, we found a stagnant pool of water directly under a large water stain in the ceiling; the water was covered with a black, mold-like mesh and smelled intensely.

3. Procedures for receiving, reviewing and evaluating complaints by a formally designated unit have not been adequately established. Specifically, you did not evaluate all complaints for investigation.

4. Written production and process control procedures are not adequate. Your firm uses an uncontrolled Excel spreadsheet as its Inventory Control System which anyone has permission to change, delete, add to, etc. As a result, your product inventory is not reliable or accurate.

Exercise #5: Supported v. Unsupported FDA-483 Responses

Below is a real-world FDA-483 observation AND the firm's response. In the space provided, determine if the response:

1) Includes a short-term, immediate fix (band-aid) that the firm implemented prior to sending in the response;
2) Has at least one longer-term fix that addresses the non-compliance in a more systemic manner;
3) Explains how these fixes will prevent further similar non-compliance.

FDA-483 Observation Your Quality Control Unit does not have enough controls to maintain complete and accurate laboratory records of analytical raw data.

Specifically, the Quality Control Unit has not established robust and scientifically sound standard procedures to control and ensure the integrity of the laboratory data associated to the chromatographic analysis for the release testing of active pharmaceutical ingredients (API), finished drug product and stability batches. Your current procedures allow for unlimited manual integrations of peaks in samples and standards during assay analyses.

> **Response** We will improve controls for integrations used during assay analyses. Integration will only be performed by the automatic processing method in the Empower 2 system. The type of integration method used, in this case automatic processing, will be indicated on each chromatogram. All analysts will be trained to follow the updated procedure. Additionally, we have performed a verification of the automatic integration method compared to the manual integration method to ensure comparability with data already generated [table showing comparable (not exactly equal) results attached].

1) What is the immediate, short-term "band-aid" fix (if any) that this firm implemented?

_____

_____

2) What are the longer-term, more systemic fixes the firm plans?

_____

_____

3) Do the solutions presented by the firm fix the problem/non-compliance and ensure no similar non-compliance in the future?

_____

Exercise #6: Supported v. Unsupported FDA-483 Responses

Below are five real-world responses sent to FDA following an inspection.

In the space provided, determined if each statement is a supported FDA-483 response that addresses the observation with supportive evidence OR is an unsupported response that will not allow FDA to determine the adequacy of the corrective and preventative actions.

For instances in which there is an unsupported response, rewrite the statement to provide the necessary support and resolutions. Use your imagination to make up any missing facts, documents, or other evidence necessary to support your revised response.

Response 1 In regards to Observation #4 that some analysts were not following the written procedure, we have retrained those analysts – and all of our analysts – on the procedure, we have instituted a formal on-the-job, dry test run using the SOP and supervised by the lab supervisor as the final part of training, and we have added an internal audit of the labs to our annual internal audit schedule.

Enclosed are the following 15 documents: the revised internal audit schedule for the next 18 months showing two different schedule audits; the documented lab supervisor's sign-off and approval of each analyst's dry run through of the SOP on the lab equipment (there are 12 sets of review and sign-offs in total); the most recent dates of retraining for all of our analysts; and a copy of the CAPA investigation and root cause analysis.

_____ Unsupported 483 response

_____ Supported 483 response

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_____ Unsupported 483 response

_____ Supported 483 response

Response 2 Regarding Observation #3 "Facility equipment used for testing and approval or rejection of components, ingredients and/or finished product were inadequate," we have retrained our Purchasing department to buy self-calibrating equipment from now on.

_____ Unsupported 483 response

_____ Supported 483 response

Response 3 Regarding Observation #12 that "Production personnel were not practicing good sanitation and health habits," we have fired the individuals you observed, so this observation is no longer valid. We have enclosed a letter from the HR manager stating the various dismissal dates.

_____ Unsupported 483 response

_____ Supported 483 response

Response 4 In regards to Observation #9, "Procedures for corrective and preventative actions have not been adequately established," we have started to draft a revised CAPA SOP (a copy of the new draft is enclosed). We have also retrained all of our staff using this current draft, just in case.

_____ Unsupported 483 response

_____ Supported 483 response

Response 5 In regards to Observation #7, "Failure to establish procedures for and maintain records of product design and validation," we keep all of those items in our email system and your investigators refused to look through the 11,000 emails we went through the trouble of making available to them during the inspection, thus we disagree with your investigators' citation.

_____ Unsupported 483 response

_____ Supported 483 response

Exercise #7: True or False

Mark each statement below as TRUE or FALSE.

1. Multiple Form FDA-483 observations always results in a Warning Letter _____
2. FDA investigators are law enforcement officers _____
3. Oral responses and assurances in the closeout meeting are sufficient to avoid further FDA enforcement _____
4. When responding to an observation on a Form FDA-483, you should provide documented proof of your corrective and preventative actions _____
5. The risk category of your product has no impact whatsoever on whether you'll receive a Warning Letter after getting a Form FDA-483 _____
6. The best tactic when pushing back on an FDA investigator in the closeout meeting is to make sure you pack the room with your employees _____
7. FDA only ever asks about data integrity when they see computers _____
8. After the inspection closeout meeting, FDA must receive your FDA-483 responses within 15 business days or less _____
9. Getting a lawyer to write and submit your responses to a Form FDA-483 is appreciated by FDA response reviewers _____
10. A good response to a Form FDA-483 observation always provides at least 1 or 2 additional "beyond the scope" corrective or preventative actions _____

About Your Presenter

John Avellanet is an award-winning FDA compliance expert known for his business-savvy, pragmatic advice and engaging, friendly style.

Mr. Avellanet trains FDA and Health Canada inspectors and district officers on advanced data integrity inspection techniques and detecting data fraud in manufacturing, laboratory and clinical operations.

He was the lead author of several certification courses on cGMP and QSR supplier management for the US Regulatory Affairs Professional Society.

He most recently co-authored the book, Pharmaceutical Regulatory Inspections (2014), along with several current and former regulatory agency officers, and his industry classic book, Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine, was originally featured at BIO 2011.

In 2011, he was asked by the US Office of Inspector General, Health & Human Services to oversee the multi-million dollar Dr. Comfort Corporate Integrity Agreement (CIA) through 2016.

And in both 2009 and 2011, Mr. Avellanet won the "Best of Business" award from the US Small Business Commerce Association. His blog, ComplianceZen.com, has been repeatedly named one of the "Top 50 Blogs" worldwide on FDA compliance.

Over the past 11 years, he has been interviewed on public radio programs, in numerous industry magazines and multiple news outlets. He speaks frequently for industry conferences and private corporate workshops.

Prior to founding his compliance consulting firm, Cerulean Associates LLC, Mr. Avellanet was a former *Fortune 50* combination device C-level executive who created, developed, and ran his company's compliance programs to achieve ISO, DEA, BIS and FDA compliance. During his career, he had to defend decisions to investigators, auditors, and litigators alike. He now brings his hard-won, real-world expertise and practical advice to his corporate clients worldwide.

A former FDA and US Department of Justice prosecutor has said of Mr. Avellanet, "He is the best in the business. Period."

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For more about working with John, visit www.Ceruleanllc.com