Investigator Insights—Preparing for and successfully facilitating an FDA Inspection

U.S. Food and Drug Administration
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Disclaimer

This presentation reflects the views of the speaker and should not be construed to represent the views or policies of the FDA.

OVERVIEW

- What Investigations is Tasked With
- Systems Based Inspections
- Other Inspectional Tasks
- FDA-483 Examples
- Electronic Systems
- Meet with Success
- Preparation / Frequent Requests

FDA Investigations is Tasked With…

- Protecting and promoting the public health
- Determining whether adherence to regulations affects ability to meet standards of quality and purity, which might otherwise render products adulterated or misbranded
- Looking for justified scientific rationale wherever it should be applied

Systems Based Inspections

- Based on Compliance Program Guidance Manual 7356.002, typically two to four rotating systems, but may overlap
- Others referenced: 7356.002A, F, M, P
- Guidance Documents demonstrate current Agency thinking, and provide suggestions, but not regulations

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm

Systems Based Inspections

- Quality (always performed)
- Production
- Facilities and Equipment
- Laboratory Control
- Materials
- Packaging and Labeling

Other Inspectional Tasks

- May also follow up or perform other inspectional tasks, to reduce the need to revisit your firm at a later date:
  - Follow-up to Consumer Complaints received by FDA
  - Follow-up to NDA Field Alert Reports submitted by or regarding your firm
  - Pre-Approval Assignments
  - Adverse Drug Event Reporting
  - Drug Quality Reports (MSBs)

Top 10 Drugs Observations (9/1/2015 – 9/1/2016)

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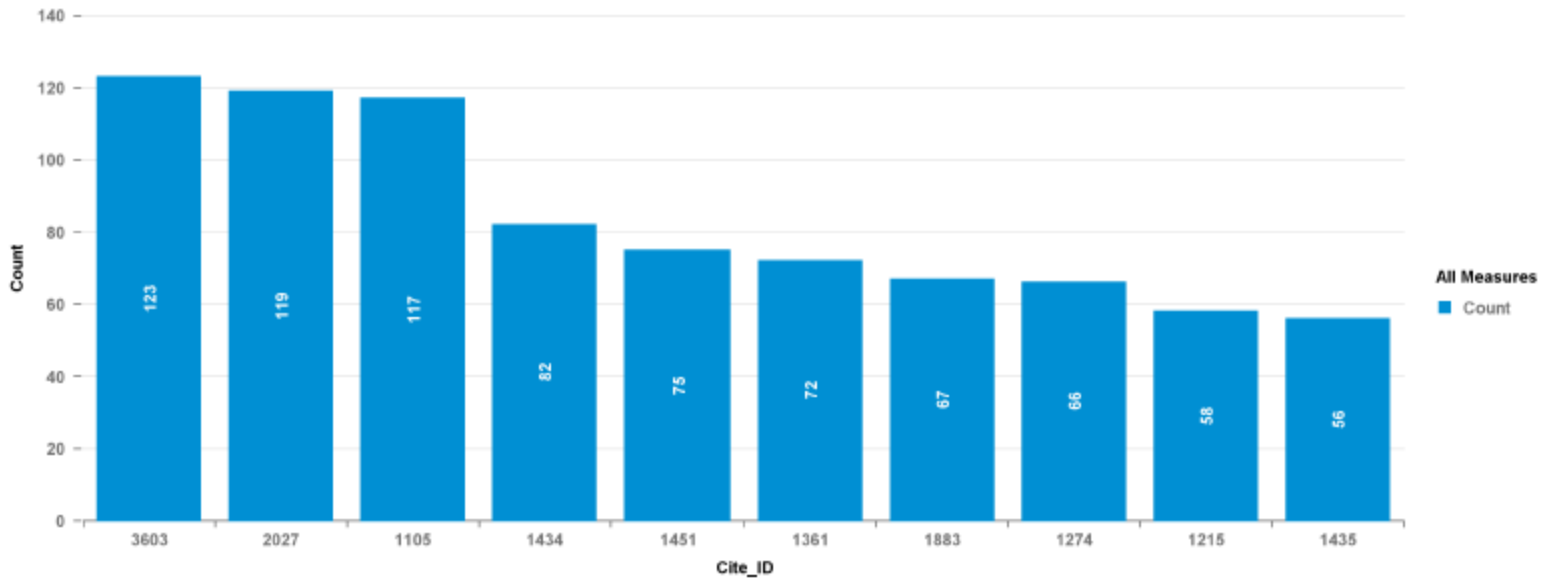
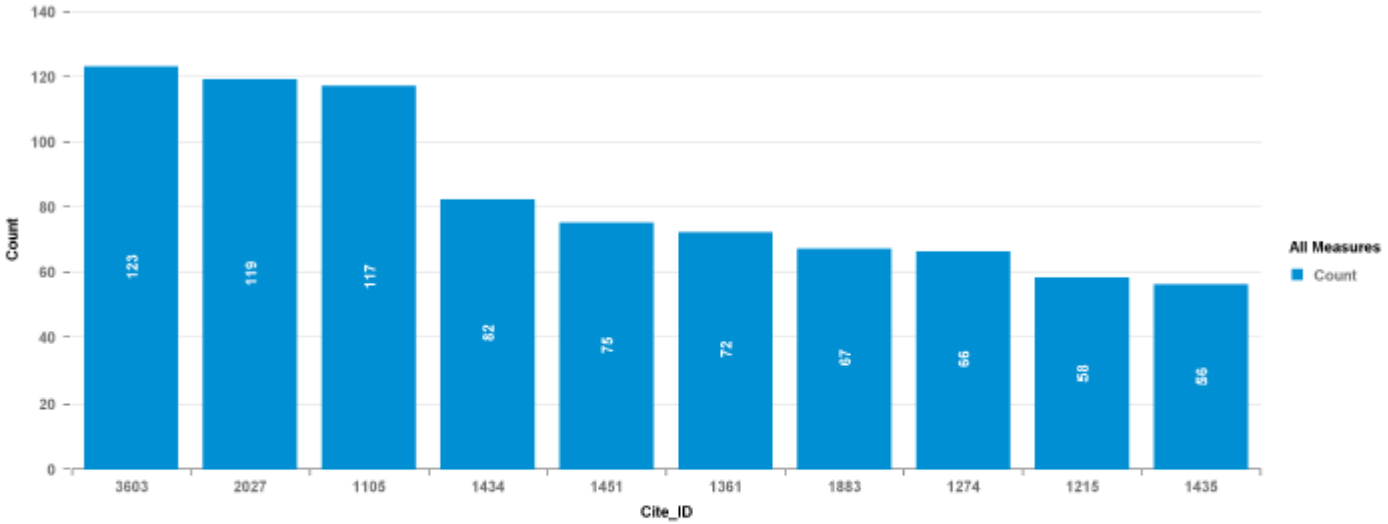


Cite ID	Count	Reference No.	Citation Text
3603	123	21 CFR 211.160(b)	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***
2027	119	21 CFR 211.192	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***
1105	117	21 CFR 211.22(d)	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
1434	82	21 CFR 211.42(c)(10)(iv)	Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically, ***

Top 10 Drugs Observations (9/1/2015 – 9/1/2016) (cont.)



Cite ID	Count	Reference No.	Citation Text
1451	75	21 CFR 211.113(b)	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***
1361	72	21 CFR 211.100(a)	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***
1883	67	21 CFR 211.165(a)	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically, ***
1274	66	21 CFR 211.68(a)	Routine [calibration] [inspection] [checking] of [automatic] [mechanical] [electronic] equipment is not performed according to a written program designed to assure proper performance. Specifically, ***
1215	58	21 CFR 211.67(b)	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically, ***
1435	56	21 CFR 211.42(c)(10)(v)	Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the [room] [equipment] to produce aseptic conditions. Specifically, ***

FDA-483 Examples

Recent FDA-483 Examples

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that components conform to appropriate standards of identity, strength, quality and purity.

Specifically, the water used in the manufacture of OTC drug products is not tested according to specifications of Purified Water, USP. Your firm does not perform Total Organic Carbon testing on a scheduled , periodic basis to ensure water component meets appropriate specifications for pharmaceutical use. Your firm's water system was observed in the manufacture of the following finished drugs which were compounded by your firm: Product X Lots 123 and 124 and Product Y Lot 134

Recent FDA-483 Examples

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A.Your firm failed to investigate microbiological contamination observed at least 53 times noted during **(b)(4)** sterility testing of sterile **(b)(4)** intended to be used in the manufacture of sterile injectable drug products, including lots of Products A, B, C, etc. In approximately 18 instances your firm retested the affected **(b)(4)** and microbiological contamination was also observed in at least one of the retest samples.

1. There is no documented evidence that suggests that a health hazard evaluation was initiated or conducted in order to assess the potential quality impact of microbiological isolates noted during the **(b)(4)** sterility testing.
2. There is no data to support your firm's claim that all the sterility failures were attributed to contamination during the performance of the **(b)(4)** sterility method.
3. There is no documented evidence that your firm implemented permanent corrective actions to prevent these sterility events from recurring.

Furthermore, approximately **(b)(4)** lots of sterile injectable drug products were manufactured and released from the affected **(b)(4)** lots.

Recent FDA-483 Examples

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch to meet any of its specifications whether or not the batch has been already distributed. (cont.)

B.Your firm failed to adequately investigate three sterility failures. For example, the following was observed regarding two 2012 sterility failures (Product X Lot 123 and 124; and Product Y Lot 125).

1. The investigation into the two sterility failures did not determine possible root causes of the contamination. Notably, it also lacked any meaningful corrective or preventive actions to prevent future non-sterility events.
2. The investigation failed to extend to all associated lots that may have been manufactured under the same inadequate practices or conditions that led to the microbial contamination of these lots.
3. Sterility test positive results were routinely considered questionable by the laboratory, and re-testing was done without justification. More specifically, when a positive result is obtained using the **(b)(4)** sterility testing method, your firm considers the initial positive to be an 'inconclusive' or 'suspect' results and performs re-testing. This is done although no laboratory cause of contamination has been identified.
4. Your firm did not adequately differentiate or subculture microbes found in sterility test positives. Both lots that failed sterility were assumed to be cocci based on observation under microscope. However despite multiple findings of contaminated units, no attempts were made to subculture the bacteria and further differentiate the microbe to determine its identity.

Recent FDA-483 Examples

The responsibilities and procedures applicable to the quality control unit are not in writing.

Specifically, there are no written procedures which define the Quality Control Unit's responsibility and authority

Recent FDA-483 Examples

Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems for aseptic processing necessary to prevent contamination or mix ups.

Specifically,

1. Your firm lacks documented evidence that your operators cleaned and disinfected the manufacturing room and equipment properly to produce aseptic conditions. Our investigators also observed that operators did not conduct cleaning and disinfection in a manner appropriate to maintain the aseptic environment.
2. Your firm lacked sufficient environmental monitoring of the critical ISO 5 clean zone, the ISO 7 aseptic processing room (in which the ISO 5 clean zone is located), and the adjacent ISO 7 support rooms.
3. Your personnel monitoring program to maintain microbiological contamination-free gloves and gowns did not include all operators who aseptically manufacture your sterile **(b)(4)** drug products.

Recent FDA-483 Examples

Your firm failed to follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes.

Your media fill record reconciliation documentation failed to include a full accounting and description of the units rejected from each batch. Although a significant number of media-filled units were rejected with no written justification, we found the following media fills runs deemed as acceptable.

Media fill batch #	*Run date*	*Filled units*	*Rejected units*
(b) (4)	October 30, 2014	(b) (4)	81
	October 27, 2014		21
	September 14, 2014		36
	August 1, 2014		249
	May 26, 2014		64
	December 20, 2013		121
	November 28, 2013		5
	November 27, 2013		35
	November 19, 2013		185

Recent FDA-483 Examples

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

A. Your firm has not validated manufacturing process for OTC **(b)(4)** drug products. The manufacture of this product involves various **(b)(4)** mixing steps **(b)(4)** but neither of these individual steps nor the complete process is validated. This product also contains **(b)(4)** which is not tested.

B. Your firm has not validated cleaning procedures for the manufacturing equipment and utensils used in the manufacture of **(b)(4)** including the mixers and blender and the filling machine.

C. Your firm has not validated or verified under actual conditions of use the testing methods which includes the determination of Viscosity, Microbial counts (total bacteria, mold and yeast, *E. Coli, Pseudomonas aeruginosa, Staphylococcus aureus*) and has no methods and does not test for **(b)(4)** ingredient.

Recent FDA-483 Examples

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

Specifically, finished product testing has not been completed to demonstrate that all manufactured and distributed **(b)(4)** drug products between February 2012 to current date meet all label claims. For example, your firm personnel could not provide any assay test data verifying that any active ingredients are present as claimed on **(b)(4)** finished drug product labels.

Electronic Systems

Part 11 Compliance

- Automatically save data (to remote server)
- Retention of complete and accurate data
- Audit trail
- Prevention from deletion or alteration
- Frequent backup to drives or disks stored elsewhere (performed by someone outside functional group)
- Automatic timeout on computers

Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application.
Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm

Data Integrity – What We See

- Not recording activities contemporaneously
- Backdating
- Copying existing data as new data
- Re-running samples
- Discarding data
- Trial injections
- No audit trail capability

Discarding Data 483 Examples

1. Failure to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records.

For example, you analyzed API lot 1234 on February 14, 2011, at 2:55 a.m., and then retested it at 2:05 p.m. using a new sample solution. You did not maintain any raw data associated with the initial test.

2. Your firm used … different HPLC processing methods to process data and did not investigate or document all these tests, and discarded raw data related to sample weights and preparations, in disregard of SOP requirements

3. Sample and reagent weights are written on small pieces of paper and transcribed onto analytical worksheets. These small pieces of paper were discarded.

FDA-483 Example

Computerized systems do not have sufficient controls to prevent unauthorized access or changes to data. There are no controls in place to prevent omissions in data.

Specifically, during our inspection of the **(b)(4)** laboratory used as an analytical support laboratory for quality and manufacturing cGMP investigations, we found that each of the **(b)(4)** HPLCs and **(b)(4)** GCs currently in use were not equipped with sufficient controls (e.g. audit trails) to prevent changes to or omission of raw data.

Our random review of one HPLC hard drive uncovered evidence that analytical raw data had been collected throughout the month of November 2014 and had been deleted. No hard copy printouts of these results could be provided, the testing was not recorded in the instrument use logbook, and the identity of the product(s) analyzed could not be determined. According to the responsible analyst, another individual had logged into the system using his credentials and had performed injections and deletion without his knowledge.

Additionally, we found that the systems are configured so that no passwords are required during log-in, including the use of the software Administrator privileges.

Facilitate an Inspection Successfully

Who Is Best To Answer Questions?

- Management can give overview of a system or program, but…
  - Personnel regularly performing a task often better to discuss how it works
  - Individuals or teams that wrote an investigation
  - Supporting staff that helped develop a product or method
  - Sharing institutional knowledge fosters better communication

Meet With Success For Your Next FDA Inspection

- If we cannot complete our assignment, the task at hand will take longer
- We recognize that you are the experts in your process and facility, additional explanation may be necessary
- We cannot take the role of consultants
- When generating electronic lists, ensure they have:
  - all requested information
  - are clear (key may be necessary)

Meet With Success…

- Incomplete or inadequate documentation that does not tell full story is problematic
  - Consider including timelines in investigations
  - Demonstrate timely follow-up, sound scientific rationale
  - Is basic information easy to find and always included in every document (part of form)?
- Provide requests as they come in

Tips for Inspectional Preparation

- Discuss with all personnel your firm's obligation to and relationship with FDA
  - Facilitate inspection, provide requested documents, make copies, avoid refusals
- Consider making one person responsible for facilitating inspection, and a backup
- Know who to contact when we arrive
  - FDA-482, Notice of Inspection → Most Responsible Person

What Can You Have Ready?

- Product list for domestic and other markets
- Firm history
- Organizational charts with personnel names (high level)
- Facility diagrams
- Index of SOPs
- List of assets (manufacturing and laboratory equipment)
- Easy access to lists of Quality Systems data
- Annual Reports
- Quality Agreements (QA)

Illustrative Scenario for QA

A Quality Agreement (QA) Does Not Exempt Contracted Facilities From CGMP Requirements Related to the Operations they Perform, Regardless of Whether Such CGMP Requirements are Specifically Discussed in the Quality Agreement

Case 1: Responsibility for Facilities and Equipment Maintenance and Upkeep at Contracted Facility

- Contracted Facility that manufactures injectable product
- Significant objectionable conditions found at the Contracted Facility related to deficient maintenance of the facilities and equipment used to manufacture the injectable product, such as defective or partially broken equipment, visibly tarnished piping, leaking seals, etc.
- Facility design is inadequate to prevent contamination.
- QA in place specifying the product Owner's responsibility for upgrades and maintenance of the facilities and equipment. The Owner fails to provide the requisite resources or carry out the necessary upgrades and maintenance, but and the Contracted Facility continues to manufacture the product under non-CGMP conditions that could result in product contamination.
- WL issued to the Contracted Facility

Lessons learned

Taken from: Guidance for Industry Contract Manufacturing Arrangements for Drugs: Quality Agreements Draft Guidance May 2013

Illustrative Scenario for QA (cont.)

Contract Laboratories are Contracted Facilities Subject to CGMP Requirements

Case 3: Responsibility for Data Integrity in Laboratory Records and Test Results

•Contracted Facility providing contract analytical laboratory services repeatedly reports passing results in its CGMP records when failures were obtained in actual analysis.

•The Contracted Facility also fails to report accurate results to its client, the product Owner.

•When FDA inspects the Owner, it is revealed that the Owner did not audit the contract laboratory prior to FDA's inspection of the Owner, despite the fact that the Owner has a written procedure in place requiring a site audit of contracted facilities every two years.

Lessons learned

Common Requests for Electronic Systems

- If requested, can provide electronic documents on CD-R if large in volume
  - Ensure document is not locked; sorting and filtering allow for faster review
  - Rewritable so that additional requests can be added to the same CD
- If requested, can prepare mechanism to show/view files in the system, rather than full paper copies for all items (e.g., laptop and projector)
  - We cannot operate your system or equipment

Build in Quality—Be Quality Minded

A firm is only as strong as its weakest system!

- Evaluate infrastructure, how are systems designed?
  - Impact assessments to expand to other products/ processes
  - Risk analysis
  - Appropriate review

Build in Quality

- If our snapshot inspection does not find a fault, does not mean non-issue
- Poor systems will eventually catch up:
  - Continued or new deviations
  - Product/time loss
  - Inability to supply market
  - Recalls

Acknowledgements

- Brian Hasselbalch, Supervisory Consumer Safety Officer/ OMPT/OPQ/OPPQ,CDER
- Nick Violand, Consumer Safety Officer, ORA

References

- Guidance for Industry – Contract Manufacturing Arrangements for Drugs: Quality Agreements. Draft May 2013.
- Guidance for Industry – Part 11, Electronic Records; Electronic Signatures — Scope and Application. August 2003.

Thank You!

See you on inspection…

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Protecting Consumers, Promoting Public Health

U.S. Food and Drug Administration

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