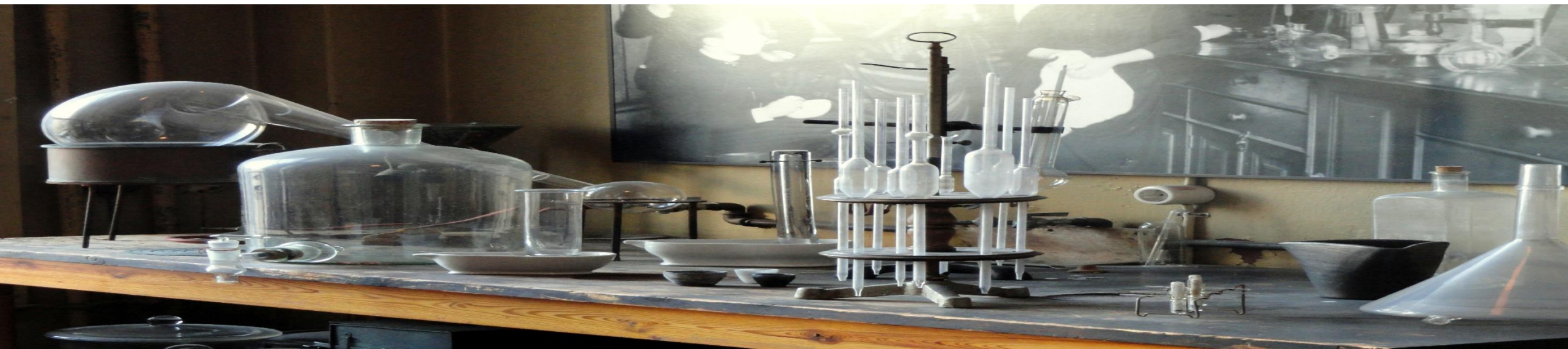


*FDA Form 483*

# No Observations on My Watch – A Practical Guide to Regulatory Agency Inspections of Analytical Laboratories

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*CE Pharm October 2, 2019*



“An F.D.A. inspection report dated July 24 to Aug. 2, 2019 noted **lapses and discrepancies in record-keeping** by the company, and **improper procedures in quality control in gathering data** on the mice.”

# The New York Times

Aug. 6, 2019

## *Novartis Hid Manipulated Data While Seeking Approval for \$2.1 Million Treatment*

“The public ‘**expects us to have accurate data when we approve products,**’ he [Peter Marks, CBER Director] added.”

“But the news that a drugmaker had **manipulated or mishandled data** is an unsettling moment for the pharmaceutical industry.”

# Objectives and Outline



Discuss common investigator concerns and some of the issues and observations that have been identified during recent analytical laboratory inspections. What should we consider to ensure compliance and usable results?

- Where to find information
- What investigators identifying during inspections – 483 trends and data integrity
- “Physiochemical Lab Inspection 101” - Notes from inspection preparation, inspections, and former and current colleagues

# Inspection Information – Regulations, Guidance, etc.



21 CFR 210 and 211 – cGMP Regulations

21 CFR 600-680 – Biological Product Regulations

ICH Q7 - Good Manufacturing Practice Guide For Active Pharmaceutical Ingredients

FDA – Compliance Program Guidance Manuals –for example, CDER PAI (Program 7346.832), Biological Therapeutic Drug Products (7356.002M), CBER (7345.848)

FDA – Q&A on cGMP Guidance Page

FDA Guidance – Analytical Procedures and Methods Validation for Drugs and Biologics

FDA Guidance - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

FDA Guidance – Data Integrity and Compliance With Drug CGMP - Questions and Answers

FDA Guidance - Part 11, Electronic Records; Electronic Signatures—Scope and Application

438 database <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations>

Warning letters <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>

# “Laboratory Controls” Section of FDA Q&A on cGMPs Guidance Page



<https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-laboratory-controls>

- 2011 guidance that is periodically updated – latest update: August 12, 2019
- Relevant old questions include:
  - Relying exclusively on auto-calibration features of equipment
  - Using an unvalidated method to test a drug component or product
- New questions include:
  - Instrument calibration standards for chromatographic systems
  - Material used for system suitability
  - Is it ever appropriate to perform a “trial injection” of samples? No...

# 483 Observations- Survey over 10 years



On average, most CDER 483s include a laboratory-related observation.

## General Themes – by frequency of observations

- Sampling plans, test procedures, and specifications to ensure conformance to appropriate standards
- Deficient laboratory records
- Facility and equipment/reagents
- Suitability for intended use
- Not following procedure or appropriately documenting and justifying deviations
- Procedure drafting, review, and approval/changes
- Computers and back-up data



From FDA Inspectional Observations database. Note: Generally does not include sampling or stability.

# Sampling plans, test procedures, and specifications to ensure conformance to appropriate standards:



- “Laboratory controls do not include the establishment of scientifically sound and appropriate specifications/standards/sampling plans/test procedures designed to assure that components/.../drug products conform to appropriate standards of identity, strength, quality and purity.”
- Acceptance criteria not adequate to assure that batches of drug products meet specification
- No description of the sampling/testing procedures used
- No determination of conformance to written descriptions of sampling procedures/ specifications
- No laboratory determination of satisfactory conformance to the final specifications/identity and strength of each active ingredient prior to release

# Deficient Laboratory Records:



Records do not include

- Complete data derived from all tests, examinations and assays
- All calculations performed in connection with the test
- Initials or signature of the person who performs each test/the date(s) the tests were performed
- Initials or signature of a second person showing that the original records have been reviewed
- Method used/location of the data that assures accuracy and reliability of the method
- Description/source/quantity/lot number or code/date of the sample
- Weight/measure of the sample used for testing
- Testing and standardization of laboratory reference standards/reagents/standard solutions.
- Statement of results of tests and how results compare with established acceptance criteria



## Facility and equipment:



- Adequate lab facilities not available to the quality control unit
- Use of instruments/apparatus/gauges/recording devices not meeting established specifications
- Equipment not suitable for its intended purposes/capable of producing valid results
- Written procedures not established/followed to ensure that the lab equipment (or automatic/mechanical/electronic equipment) is routinely calibrated/inspected/checked/maintained
- Calibration procedures do not include specific directions/schedules/limits for accuracy and precision/provisions for remedial action
- No document/complete record of the calibration/inspection/maintenance of laboratory equipment/laboratory instruments...
- Calibration not done at suitable intervals with established program/provisions for remedial action
- Identity/quality of reagents/solutions/supplies used in testing procedures not adequately controlled

## Suitability for Intended Use:

- Analytical methods not suitable for their intended use/sufficiently sensitive/specific/accurate/reproducible
- Accuracy/sensitivity/specificity/reproducibility of test methods/new test procedure implemented in a specification have not been established/documentated
- Verification of the suitability of the testing methods not performed under actual conditions of use/documentated
- Not first verify/document that a compendial test procedure works under the conditions of actual use
- Records of modification of an established method not include reason for the modification/data to verify the modification produced results that are at least as accurate and reliable for the material being tested

## Not following procedure and not appropriately documenting and justifying deviations:

- Established specifications/standards/sampling plans/test procedures/laboratory control mechanisms not followed/documentated at the time of performance
- Deviations not recorded/justified
- *Investigations of unexplained discrepancy/failure of a batch or components to meet specifications not extend to other batches/other drug products that may have been associated with the failure or discrepancy*

## Procedure drafting, review, and approval/changes:



- Written procedures/changes not drafted, reviewed, and approved by the appropriate organizational units/quality control unit
- Establishment of specifications/standards/sampling plans/test procedures/laboratory control mechanisms and change not drafted by the appropriate organizational unit/reviewed and approved by the quality control unit
- Complete records not maintained for modification of established method

## Computers and back-up:



- Input to and output from the computer/related systems of formulas/records or data not checked for accuracy
- Failure to maintain backup file of data entered into the computer or related system
- Backup data not assured as exact/complete/secure from alteration, erasure or loss through keeping hard copy or alternate systems

# Data integrity – More Problematic or More Awareness



- 1980's: Substantial falsified generics data submitted to FDA -> evaluation of raw data during inspections
- 1997: 21 CFR Part 11 – “Electronic Records and Electronic Signatures”
- 2010: Data integrity focus announced
- Number of warning letters that include data integrity issues increases each year (FDAZilla):
  - 2017 56/70
  - 2018 69/91
- Sites world-wide and across industry

# Data Integrity – A Very Public Issue



## Apotex:

(warning letter from the FDA for inadequate OOS investigations and for lacking valid in-process specs)

Federal Register- July 3, 2019

“The Food and Drug Administration (FDA or Agency) is **withdrawing the approval of 31 abbreviated new drug applications** (ANDAs) held by Apotex, Inc. (Apotex). Apotex, through its U.S. agent, has requested withdrawal of these applications and has waived its opportunity for a hearing.”

## Akorn:

Reuters – April 22, 2018: Fresenius **pulls out of Akorn takeover** over data integrity

“... could terminate the deal if its own independent probe found Akorn breached U.S. Food and Drug Administration data integrity requirements related to product development.”

FiercePharma - Aug. 1, 2019

“After Fresenius deal collapse, Akorn inks **\$74M settlement with investors** over data integrity woes.”

# Data Integrity – A Very Public Issue



FDA Press Release Aug. 20, 2019 - Acting FDA Commissioner Ned Sharpless, M.D.

“Americans deserve to have confidence in the quality of drugs the FDA regulates – from the prescription medicines they take to the over-the-counter products they use in their daily lives, like toothpaste and sunscreen. Helping assure the quality and safety of these products is one of our greatest responsibilities as a public health agency. In recent years, the FDA has focused additional resources on efforts to prevent, uncover and combat data integrity lapses. We’ve focused comprehensive new efforts on these risks, both through our global inspections program as well as providing updated guidance, and to train our staff on identifying concerns related to data integrity.”



# Data integrity – FDA



Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

Data integrity is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record's retention period ends.

System design and controls should enable easy detection of errors, omissions, and aberrant results throughout the data's life cycle.

# Data integrity – FDA Inspection

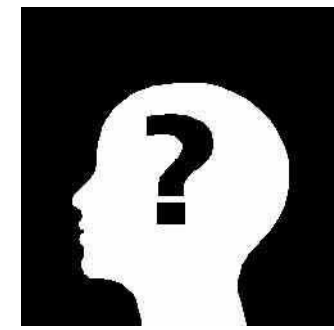


FDA Compliance Program Guidance Manual; Chapter 46- New Drug Evaluation (Subject Pre-Approval Inspections) provides detail.

## Objective 3: Data Integrity Audit

- Audit raw data (e.g., chromatograms, spectrograms, laboratory analyst notebooks) to authenticate data submitted in the application. Verify that all relevant data were submitted....
- Any “passing” data substituted in place of “failing” data without a sufficient investigation? Improper invalidation of OOS results?
- List of possible indications of data integrity problems
- Examples of data integrity problems that have been previously observed:
  - Multiple analyses of assay with the same sample without adequate justification
  - Exclusion of specific lots from the stability program; backdating stability test results
  - Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
  - Creating acceptable test results without performing the test
  - Using test results from previous batches to substitute testing for another batch

# Lab Inspection 101 – What is an investigator thinking?



Lists similar to compliance manuals

How do sites/quality systems deal with problems when they arise?

How proactive are sites/quality systems at identifying and mitigating potential problems?

# Lab Inspection 101 – Issues and Issue Prevention



Deviations (discrepancies, events, etc.) including OOS (or OOT)

Deviation/OOS and Investigation, CAPA, Change Control, Trending/Tracking, Annual Product Review, Training, Equipment Qual./Maint./Calibration... procedures

- Are they appropriate?
- Are they being followed routinely?

OOS SOPs:

- How/when is retesting/re-sampling (or use of retain) allowed?
- How are reportable results calculated?
- Closed loop is required – no infinite retesting.

**483 Observations**

- ❖ **Invalidating OOS results without justification; use of an outlier test for invalidating OOS, then average results from any testing**
- ❖ **Resampling or re-injecting when OOS results obtained- no investigations**

# Lab Inspection 101 – Methods – Current SOPs



Inform lab tour discussions

How are the SOPs drafted/approved/updated?

How are the SOPs and related worksheets controlled?

Integration

- Automated vs Manual - “rules” and potential for manipulating into spec
- Saving of original data and changes (data integrity)

Are all the appropriate controls in place and monitored

- Requirement for e-gram consistency with reference documented?
- If there is a common/known failure, is that included as an example?

System suitability- Is it appropriate for the method (and product) = suitable for its specific use?

**483 Observations**  
**❖ SOP allowance for discarding data**

# Lab Inspection 101 – Methods – Paper Review



Compendial methods: Verification of performance at that site and with that product

Transferred methods:

- Was transfer done appropriately?
  - Sufficient number and types of samples?
  - Comparison to results at originating lab?
- Review protocol vs performance and raw data vs transfer report

# Method Transfer Woes

(currently more often lack of approvability issue vs 483 observation)



No direct comparison to the originating lab (partial validation, no “useful” indirect comparison).

Electropherogram profile compared to the example included in the method SOP. However, the specifications also include quantitative criteria.

Quantitative method receiving lab results for one sample (mean) compared to the historical originating lab results for “the same sample material.”

Comparison included only a sample with very low levels of impurities.

Only acidic variants had established transfer criteria.

The method transfer study should:

- Demonstrate that method performs as expected in the receiving laboratory- ability to detect and quantify lot-to-lot differences or changes during storage.
- Demonstrate equivalence between the originating and receiving labs.

# Lab Inspection 101 – Lab Tour – Not Just the Laboratories



Beginning to End = Samples, Reagents, Equipment, Method, Performance, Data, Results

Sample:

- Sampling plans/collection/submission/management/tracking – chain of custody SOPs
- Storage conditions and times, transfer, aliquoting
- Observe storage areas, sample processing into computer system (e.g., LIMS) or paper system, tracking from manufacturing to labs to reserve/retain.

**483 Observations**

**❖ No sample traceability**

**❖ Untested samples identified**

**❖ Questionable storage conditions**

Refrigerators/freezers/chambers for critical reagents (including RS), samples, stability:

- Calibrated, alarm system, back-up storage
- Observe organization and labeling of all reagents, logbooks, freezer calibration/maintenance



# Lab Inspection 101 – Lab Tour



Reagents (Critical Reagents often listed in SOP or identifiable in SOP or validation report):

- Observe storage, labeling, expiration dating, calibration of controls
- How are critical reagents prepared and controlled?
  - Additional SOPs for critical reagents (e.g., preparation or qualification)
  - Inventory, special storage
- Critical reagents (or equipment) listed as “or alternative” - procedure for assessment

Reference Standard:

- Observe long term and temporary (in use) storage, labeling (does RS in use match lot in BLA, expiry match), storage (controlled access?), logbook/inventory
- Procedure for low RS supply, receipt from another site

Equipment (“Critical” equipment often identifiable in SOP or validation report):

- Assess qualification, calibration, maintenance, including logbook check
- Same instruments as included in validation and SOP?
- Observe logbooks/other for use and analyst training
- Observe labeling for calibration and maintenance
- Capillary electrophoresis methods
  - Capillary cutting, capillary coating
  - Routine instrument cleaning
  - Autosampler temperature, number of samples, bracketing controls, sample stability

**483 Observations**  
**❖ Equipment that has never been calibrated**

# Lab Inspection 101 – Small “Issues” That Grow: A Mash-Up Example of an Investigator’s Process



Thermometer controlling temp for sample prep calibrated to  $\pm 2^{\circ}\text{C}$ ; per method SOP, incubation at  $\pm 1^{\circ}\text{C}$  = Equipment not suitable for its purpose.



Why was thermometer not calibrated to  $\leq \pm 1^{\circ}\text{C}$ ?



Equipment maintenance list says  $\pm 2^{\circ}\text{C}$ . Why does the list say  $\pm 2^{\circ}\text{C}$ ?



List generated against originating lab version of SOP. 1) Why were SOP conditions tightened for this critical step – problems observed? 2) Why wasn't originating lab version also updated? 3) Who reviewed maintenance list for this lab at this site?



Study of  $\pm 2^{\circ}\text{C}$  = no assay issues. Change was a mistake. 1) Process for Protocol Drafting/Change Controls? 2) Who signed off on the method SOP? Did they read and have knowledge of the method? 3) What is the protocol for review? Was it followed?

# Lab Inspection 101 – Lab Tour - Testing



Observe performance of key tests

- SOP pre-review → questions for analysts re procedure, lack of clarity/instruction, dealing with samples and critical reagents/controls and instruments/equipment
- SOPs used during testing– paper copies in lab, on computer, printed from computer? How are versions updated for lab copies?
- Worksheets/results
  - All electronic or paper, too – how tracked?
  - Info (e.g., for RS or control) copied in vs pre-populated from computer system

**483 Observations**  
**❖ Operating conditions/parameters for analysis not documented**

Discuss/assess analyst (and supervisor) training

Discuss system suitability/assay failures/invalidated assays- Assessment and Trending

# Lab Inspection 101 – Lab Tour- Data and Results



## Computer

- Who has access to data and how is access controlled?
- Audit trail?
- Validated server? Backup?
- Part 11 Compliance?

**483 Observations:**  
❖ Failure to retain raw data  
❖ 1 computer account – 2 analysts  
❖ System admin rights for inappropriate users

## Data

- Complete, Authentic, Reliable
- View current and old data on server (or lab notebook)
  - Is it as expected? Compare release and stability? System suitability?
  - How were results calculated? How was integration performed? When/by whom/per SOP?
  - Data that have been modified obvious? How/when/by whom?

Results- Comparison to acceptance criteria and to reporting (e.g., in application)

How are testing/data/results documented and reviewed? Appropriate sign off?

## Other CE-Related Questions Regulators Have Asked

How does this software work?

How is signal to noise calculated? What are these fluctuations?

“Corrected” peak area? How can it be acceptable to correct the peak area?

What if the (pI, size) markers cover up important impurities/variants/peaks? How do you not miss peaks because they get “hidden” by the markers?

The e-grams do not line up. Is there a problem with repeatability? How can you be sure that the peaks in sample 1 are the same as the peaks in sample 2? (translation: How big a difference in retention time is acceptable? How do you know?)

Communication with investigators → How a site operates

Prepared, Scientific, Straightforward, Upfront, Knowledgeable, Efficient, Patient





# Acknowledgements

Current and Former Colleagues



***Doing now what patients need  
next***