FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

Investigator's Insight on the Laboratory System

By Doan T. Nguyen, Pharm D
Drug Investigator

Objectives

- Identify laboratory areas covered during an inspection
- Identify laboratory records covered during an inspection
- Regulations and citations related to laboratory
- Top laboratory violations for drugs

Laboratory System Impact

- Relates directly to Manufacturing operations
  - Blending validation
  - Cleaning validation
  - Release of Raw materials
  - Release of Production lots
  - Stability testing
- May result in denial of submissions
- May result in regulatory actions

Types of Laboratories

- Animal
- Microbiological
- Chemical & Physical
  - Raw material
  - In-process
  - Finished Product
  - Stability

FDA considers Contract Laboratories to be an extension of the manufacturer. (21 CFR 200.10)

Laboratory Inspection

Common document request:

- List for last 2 years or since last FDA inspeciton
  - OOS/OOT – Laboratory Investigations
  - Deviations – Manufacturing Investigations
  - Stability Summary
- List of All Laboratory Equipment
- Procedures for
  - OOS, OOT, Deviations, etc.
  - Stability Program
  - Instrument Calibration & Qualification
  - Method Validation & Transfer SOP

Laboratory Inspection

- **Walk Through**
  - Sample flow, condition of laboratory
  - Equipment- HPLC, software, incubators, etc.
    - Maintenance records, Logbooks, QA stickers
  - Reagents / Solutions dated
    - Eg. Expired Reagents used to prepare growth media
  - Reference Standards
  - Stability Chambers & Reserve Sample Room
  - Air handling-HEPA, Air pressure between classified cleanrooms

Document Control

- Controlled Documents
  - Validation protocols & reports
  - Methods, version control
  - OOS Investigation forms, reviewed and signed
  - Notebooks/Worksheets/Raw Data
  - Logbooks, issued and archived
- Other documents reviewed
  - Annual reports
  - Trend OOS, OOT, nonconformance's, etc.
  - Trend Stability – failing or near failing

Laboratory Inspection

- Overall management overview of control
- FARs, Recalls, MedWatch
- Data Review
  - Methods, Specifications
  - Raw Data
    - Data sheets: notebooks, numbered pages
    - Associated Data:
      - Chromatograms, Standard Prep, Qualification of Standards, Instrument Printouts

Data Recording

- How is raw data controlled
- How is data maintained
  - Bound books
  - Data sheets
  - Electronic
- Traceability
- Review & approval

5 Citations on Data Recording

- **Per 21CFR 211.194(a)** All Data obtained (including meta-data)
  - Eg of meta-data issue.
  - Sample Description: includes date received in lab, where sample taken, lot number, and quantity
  - Method used & traceability to verification or validation
  - All data from lab instruments, Calculations: units of measurements, equivalency factors, conversion factors
  - Results of Test – Pass or Fail
  - Signature/Initials of Analyst & Date tested, Reviewer
    - Accuracy, Completeness, & Compliance
- Refer to Dec 2018 Guidance on Data Integrity and Compliance With Drug CGMP Questions and Answers

Citations on Data Recording

- **Per 21CFR211.194(b)** complete record of modification to method
  - Must have documentation why method was modified.
  - Must have documented data to show modified method results are as accurate and reliable as established method

Citations on Data Recording

- **Per 21CFR211.194(c)** complete record for standards
  - Standard Identification & Preparation
    - Standardization of Reference Standard
    - Qualification of Secondary Standard
  - Standardization of Reagents & Volumetric Solutions

Citations on Data Recording

- **Per 21CFR211.194(d)** complete record of modification to method
  - Must have documentation of periodic calibration of laboratory equipment

- **Per 21CFR211.194(e)** complete record of all stability testing

  - Stability testing is required in 211.166
  - 211.194 is the data recording aspect

Data Integrity

- **Raw data vs. submitted data:**
  - Applications, Annual Reports, Responses to FDA
- **Calculation Spreadsheets** – validated and locked
- **Real Chromatograms vs. Representative Chromatograms**
- **Audit Trails**
  - Original data not overwritten
  - Access levels for software
  - Documented changes
    - Modification of method, Moving of files, deletion

Regulations

21 CFR 211

- Subpart I – Laboratory Controls
  - 211.160 General requirements.
  - 211.165 Testing and release for distribution.
  - 211.166 Stability testing.
  - 211.167 Special testing requirements.
  - 211.170 Reserve samples.
  - 211.173 Laboratory animals.
  - 211.176 Penicillin contamination

Regulations

211.160 General Requirements

- Laboratory Controls
- Sampling
- In-Process Samples
- Retesting
- Calibration
  - Written program
  - Predefined intervals
  - Remedial action
  - Specifications

Regulations

211.165 Testing and release for distribution.

- Testing and release for distribution
- Radiopharmaceutical testing
- Microbiological testing
- Sampling and testing plans with acceptance criteria
- Test methods
- Reprocessed drug products
- Failing drug products

Regulations

211.166 Stability testing

- Written program
- Sample size
- Test intervals
- Stability sample storage conditions
- Testing in same container - closure system
- Testing of reconstituted drugs
- Accelerated stability studies
- Adequate number of batches on stability
- Valid stability test methods

Regulations

211.167 Special testing requirements.

211.170 Reserve samples.

211.173 Laboratory animals.

211.176 Penicillin contamination

21 CFR 211

- Subpart J Records and Reports
  - 211.192 Production record review
  - 211.194 Laboratory records.

Regulations

211.194 Laboratory records.

- Complete test data included in records, Description and Identification of Samples, Sample identification and other information, Laboratory Test Method Verification, Test methods ID and data location, Reference and method not stated, Suitability of testing methods verified, Weight or measure of sample

211.194 Laboratory records

- Test method modification recorded Testing and standardization of standard, Laboratory equipment calibration records, Stability testing, Calculations

Guidances and Resources

- **Guidances**
  - Dec 2018, Data Integrity and Compliance With Drug CGMP Questions and Answers
  - Feb 2018, Microbiology Data for Systemic Antibacterial Drugs —Development, Analysis, and Presentation
  - Sep 2004, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- **Compliance Program Guidance Manual (CPGM)**
- **USP Methods**
- **PDA Technical Reports**

Top 10 Laboratory Violations for Drugs on 2017

CFR 211.160(b) Cite ID 3603

- 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.
- #2 Citation since 2016
- Cited 124 out of 694 citations in the FDA 483s

Top 10 Laboratory Violations for Drugs on 2017

- 21 CFR 211.192 Cite ID 2027

- 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.
- #3 Citation since 2016
- Cited 100 out of 694 citations in the FDA 483s

Examples for CRF 211.192

- Ineffective corrective and preventative actions implemented to reduce the following:
  - **Human errors**

Year	Total Laboratory cases	Human error/execution
2017	415	62%
2018	668	69%

  - **Unconfirmed OOS cases**
- 2018: 60% OOS cases unconfirmed reason
- 2017: 60 % OOS cases unconfirmed reason
  - **Invalidated OOS (WL)**
- Invalidated nearly all (134 out of 139) initial OOS results and attributed them to laboratory error. Did not conduct a full-scale investigation to thoroughly review potential manufacturing causes and assess commercial history to identify similar instances of high variation or OOS results.

Terms Used for Laboratory Errors

- There is no assurance all laboratory errors are investigated, tracked, and trended, to correct and prevent reoccurrence.
    - **Invalids, retesting, non-conformance, gross laboratory errors** are not reviewed in the same manner as OOS cases.
- Root Cause Issues:
  - **Instrument error-** if maintained appropriately and test methods are validated there should be no error with the machine
  - **Sample/product error-** can not blame the sample-OOS or human error in processing the sample

Top 10 Laboratory Violations for Drugs on 2017

- **21 CFR 211.165(a)** Cite ID 1883
- 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.

- **#6 Citation** 64 out of 694 Form FDA 483s

Top 10 Laboratory Violations for Drugs on 2017

- **21 CFR 211.166(a)** Cite ID ID 1914
- There is no written testing program designed to assess the stability characteristics of drug products.

- **#10 Citation** 61 out of 694 Form FDA 483s

Other Common Drug Laboratory Violations in 2017

21 CFR 211	Cite ID	Description	Ranking	# of 483s
211.165(a)	1883	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	#7	64
211.68(b)	1263	Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.	#8	62
211.68(a)	1274	Calibration/Inspection/Checking not done	#10	61

Other Common Drug Laboratory Violations in 2017

21 CFR 211	Cite ID	Description	Ranking	# of 483s
211.194(a)	2031	Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.	#22	39
160(a)	1810	The establishment of [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] including any changes thereto, are not [drafted by the appropriate organizational unit] [reviewed and approved by the quality control unit].	#27	29
211.167(a)	1932	Each batch of drug product purporting to be [sterile] [pyrogen-free] is not laboratory tested to determine conformance to such requirements	#28	28

The Most Common Citation

Procedure Issues

- **#1**: 21 CFR 211.22(d)-Procedures not in writing, fully followed
- **#4**: 21 CFR 211.100(a)-Absence of Written Procedures
- **#5**: 21 CFR 211.67(b)-Written procedures not established/followed
- **#9**: 21 CFR 211.113(b)-Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed].
- **#11:** 21 CFR 211.166(a)- Lack of written stability program
- **#12**: 21 CFR 211.110(a)-Control procedures to monitor and validate performance

Procedure Issues Cont.

- **#15**: 21 CFR 211.25(a)- Training--operations, GMPs, written procedures
- **#17**: 21 CFR 211.165(e)-The [accuracy] [sensitivity] [specificity] [reproducibility] of test methods have not been [established] [documented].
- **#20**: 21 CFR 211.100(b)-SOPs not followed / documented
- **#31**: 21 CFR 211.160(a):Established [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] are not [followed] [documented at the time of performance].

  – An example of this would be not recording microbial review for the exact day and time of count for each review.

Importance of Training

- Properly assess skills, not just reading SOP
- Investigation
  - Identify if employee was trained on procedure, if SOP or method needs to be updated
- Retraining
  - How did the incident occur, how to prevent from reoccurring
  - Retrain on particular skill or procedure

Quality Control

- Quality assurance is a good practice in the manufacture of pharmaceutical products

- An obligation that ensures manufacturers meet the needs of end-user needs in terms of safety, quality, efficacy, strength, reliability and durability

211.22 Responsibilities of Quality Control Unit

- (a) There shall be a quality control unit that shall have the **responsibility and authority to approve or reject all components**…and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been **fully investigated.** …be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
- (b) **Adequate laboratory facilities for the testing and approval (or rejection)** of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.
- (c) The quality control unit shall have the responsibility for approving or rejecting **all procedures or specifications** impacting on the identity, strength, quality, and purity of the drug product.
- (d) The responsibilities and procedures applicable to the quality control unit **shall be in writing;** such written procedures shall be followed.

References

- CDER Guidance
  - http://www.fda.gov/cder/guidance/
- CFR
  - https://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm
- Enforcement Actions List of 483 Citations
  - https://www.fda.gov/ICECI/Inspections/ucm589892.htm

Acknowledgment

Michele L. Obert
Drug Specialist
michele.obert@fda.hhs.gov

Simone Pitts
National Drug Expert
Simone.Pitts@fda.hhs.gov

THANK YOU!