



PDA/FDA Inspection Trends

Edmund Mrak

Investigator, Pharmaceutical Inspectorate

US FDA New England District

edmund.mrak@fda.hhs.gov

Objectives

- Introduction
- Inspection Trends: FDA-483 citations and cGMP W/L issues
- Data Integrity
- Inspection Trends: Changes in FDA
- Risk Based Assessments
- Operational Excellence

International Human/Animal Drug Inspections:

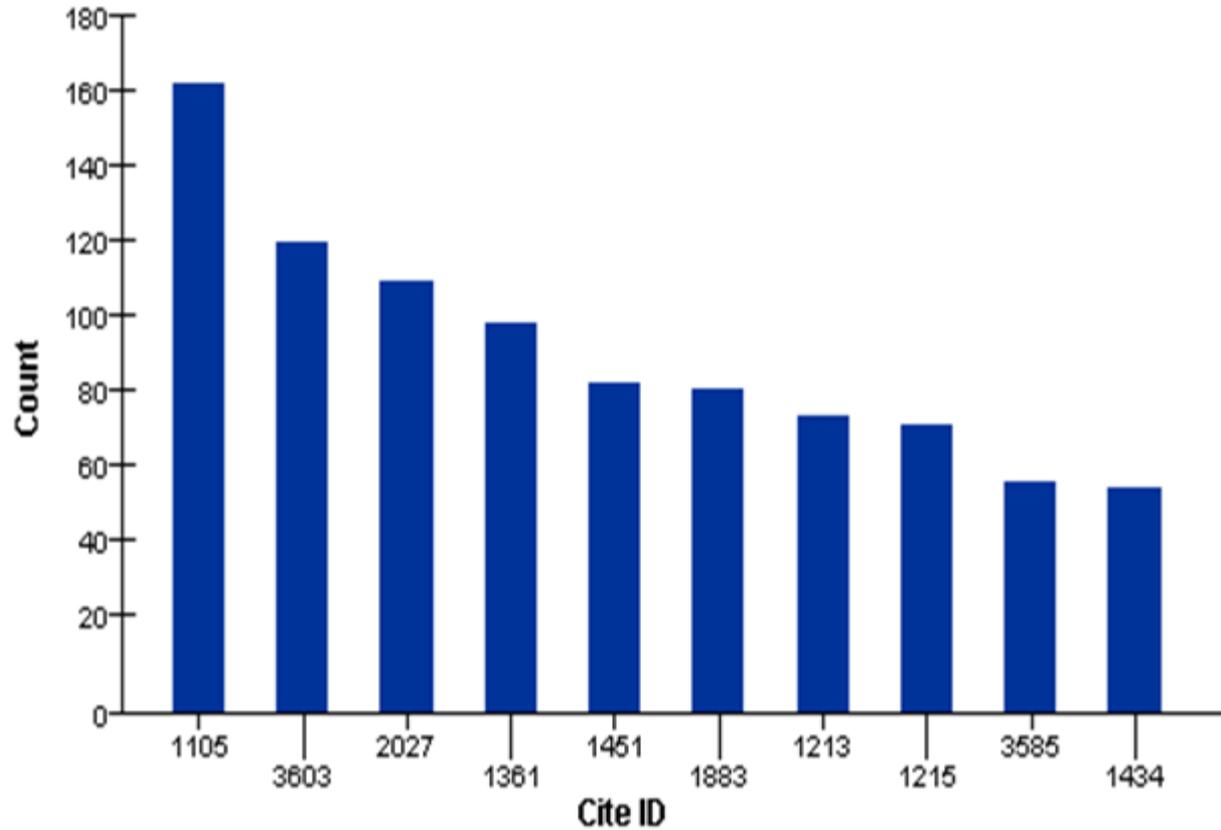
- FY 2010: 664 (+50 animal)
- FY 2011: 741 (+45 animal)
- FY 2012: 835 (+65 animal)
- FY 2013: 827 (+59 animal)
- FY 2014: 1005 (+72 animal)

Domestic Human/Animal Drug Inspections:

- FY 2010: 2141 (+286 animal)
- FY 2011: 2372 (+293 animal)
- FY 2012: 2222 (+304 animal)
- FY 2013: 1881 (+299 animal)
- FY 2014: 1875 (+229 animal)



Top 10 Drugs Observations Used in Turbo EIR Between 01/01/2014 And 03/03/2015 As of 03/02/2015





Cite ID	Count	Reference No.	Citation Text
1105	162	21 CFR 211.22(d)	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
3603	121	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	111	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, ***
1361	100	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, ***
1451	85	21 CFR 211.113(b)	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***



1883	83	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, ***
1213	76	21 CFR 211.67(a)	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, ***
1215	74	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, ***
3585	59	21 CFR 211.110(a)	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***
1434	58	21 CFR 211.42(c)(10)(iv)	Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically, ***

FY Trends for Top 10 Turbo Citations

10/1/13 – 09/30/14	10/1/12 – 09/30/13	10/1/11 – 09/30/12	10/1/10 – 09/30/11
• 211.22(d)	• 211.22(d)	• 211.22(d)	• 211.22(d)
• 211.160(b)	• 211.192	• 211.100(a)	• 211.100(a)
• 211.192	• 211.100(a)	• 211.192	• 211.160(b)
• 211.100(a)	• 211.160(b)	• 211.160(b)	• 211.192
• 211.67(b)	• 211.113(b)	• 211.110(a)	• 211.67(b)
• 211.113(b)	• 211.67(b)	• 211.67(b)	• 211.100(b)
• 211.165(a)	• 211.67(a)	• 211.68(a)	• 211.25(a)
• 211.67(a)	• 211.165(a)	• 211.100(b)	• 211.67(a)
• 211.68(a)	• 211.166(a)	• 211.67(a)	• 211.165(a)
• 211.166(a)	• 211.110(a)	• 211.25(a)	• 211.110(a)

Quality System

W/L GMP Citations FY'14 & FY'15

<u>Cite</u>	<u>Details</u>
#1 211.192	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.
#2 211.25(a)	Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations].
#3 211.22(a or d)	a. There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, 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. The QCI shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. d. The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.



Laboratory Controls System

W/L GMP Citations in FY'14 & FY'15

<u>Cite</u>	<u>Details</u>
#1 211.194(a)	Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays.
#2 211.160(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.
#3 211.160(a)	Deviations from written [specifications] [standards] [sampling plans] [test procedures] [laboratory mechanisms] are not [recorded] [justified]; Established [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] are not [followed] [documented at the time of performance]; 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].
#4 211.165(a or e)	a. There shall be appropriate laboratory determination of satisfactory conformance to final specs of the drug product. e. The accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).



Production System

W/L GMP Citations FY'14 & FY'15

<u>Cite</u>	<u>Details</u>
#1 211.100(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.
#2 211.188(b)	Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include: documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished...



Material System

W/L GMP Citation for FY'14 & FY'15

Cite

211.84(a)

Details

Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the **quality control unit**.

Facilities & Equipment System

W/L GMP Citation for FY'14 & FY'15

Cite

Details

#1 211.68(b)

Appropriate controls shall be exercised over computer or related systems **to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from computer or related system of formulas or other records or data shall be checked for accuracy...A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes.** In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that back data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

#2 211.67(b)

Written procedures shall be established and followed for cleaning and maintenance of equipment.

Before we review excerpts from a few warning letters issued in 2015 - Why is Data Integrity Important?

Data integrity breaches:

- undermine assurance of pharmaceutical quality (and potentially safety and efficacy)
- break down basic trust with regulator and public
 - *The regulatory system largely relies on trusting people to routinely do the right thing (i.e., when the regulator is not there watching)*
- **are a fundamental failure of the Quality System**

Data Integrity

Laboratory

- The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted.
- Data deleted or altered, with no audit trails.
- Backdating; rewriting or destroying lab notebooks.
- Password sharing.
- Selection of only passing results from HPLC and GC (gas chromatography) data, while failing test results are disregarded, ignored, and not investigated. This practice was noted during the testing of raw materials, finished drug release and stability studies.

Data Integrity

- Manufacturing
 - Torn Batch Production Records found in a trash can. Upon further follow-up, we found that batches had failed blend uniformity testing
 - Records (e.g., batch, training) fabricated during the inspection.
 - Shadow/Show factories; equipment removed during inspection.
- Management Oversight
 - Senior Management informed FDA investigators that they were unaware of the data breaches
 - *Your Senior Management, at the local and corporate levels, is responsible for assuring that strict corporate standards, procedures, resources, and communication processes are in place to detect and prevent breaches in data integrity, and that such significant issues are identified, escalated, and addressed in a timely manner.*

Excerpts from 2015 WL's - Office of Manufacturing Quality - Data Integrity

Inadequate controls of your computerized analytical systems raise questions about the authenticity and reliability of your data and the quality of your APIs. It is essential that your firm implements controls to prevent data omissions or alterations. It is critical that these controls record changes to existing data, such as the individuals making changes, the dates, and the reason for changes. For example:

- a) There is no assurance that you maintain complete electronic raw data for your Gas Chromatography (GC) instrument. FDA investigators observed multiple copies of raw data files in the recycle bin connected to the GC instrument QC-04 even in the presence of "Do Not Delete Any Data" notes posted on two laboratory workstation computer monitors.
- b) Employees were allowed uncontrolled access to operating systems and data acquisition software tracking residual solvent and moisture content. Our investigators noted that there was no password functionality to log into the operating system or the data acquisition software for the GC, the High Performance Liquid Chromatography (HPLC) instrument QC-17, or the Karl Fischer (KF) Titrator QC-13.
- c) HPLC SpinChrome and GC Lab Station data acquisition software lacked active audit trail functions to record changes in data, including original results, who made changes, and when.

Excerpts from 2015 WL's - Office of Manufacturing Quality - Data Integrity

You failed to have proper controls in place to prevent unauthorized manipulation of your laboratory's raw electronic data. Our inspection revealed your HPLC system did not have access controls to prevent alteration or deletion of data. Your HPLC software lacked an audit trail recording any changes to the data, including: previous entries, who made changes, and when changes were made. During the inspection, we also noted that all laboratory employees shared a common log-in and password to access the system.

This lack of control over the integrity of your data raises questions about your analytical data's authenticity and reliability, and about the quality of your APIs.

Excerpts from 2015 WL's - Office of Manufacturing Quality - Data Integrity

- Our investigators observed specific deviations during the inspection, including, but not limited to:

Failure to record activities at the time they are performed and destruction of original records. Specifically, your employees completed batch production records entries days after operations had ended, released lots before the proper approvals, and failed to maintain original manufacturing data for critical steps in the batch production records. For example,

a) Our investigators found that some of your operators used “rough notes” (unbound, uncontrolled loose paper) to capture critical manufacturing data and then destroyed these original records after transcription into the batch production records.

Trends in FDA

The Reorganization of FDA ORA (Office of Regulatory Affairs) is on-going. Inspection operations have been divided into six areas: drugs, biologics, medical devices, bioresearch monitoring, tobacco and human and animal food products with a goal to achieve greater consistency across inspections.

The drug specialty may be divided into additional subspecialties, including APIs, sterile products and pharmacy compounded products.

Risk Based Assessments

PIC/S (Pharmaceutical Inspection Convention (Cooperation) Scheme – October 2015

We are not only evaluating whether firms are using formal risk assessments to make decisions regarding such things as IPC's, environmental controls, procedures, and environmental monitoring, but are the firm's risk assessments robust (i.e. is the risk question or problem accurately defined), logical, and based on good scientific data.

Is the outcome logical?

Risk Based Assessments

ICH Q9:

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

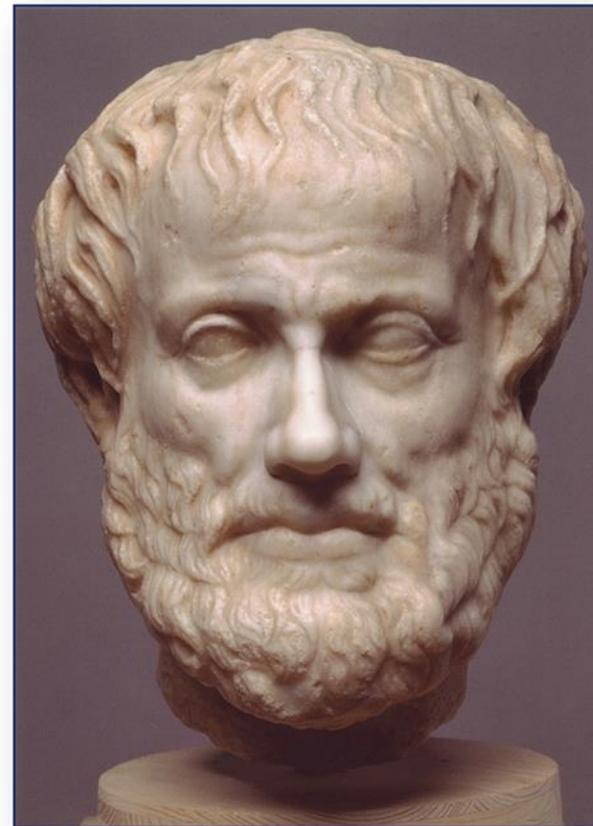
Diagram of the ICH Q10 Pharmaceutical Quality System Model



Operational Excellence

“We are what we repeatedly do. Excellence, then, is not an act but a habit.”

- Aristotle



Operational Excellence

- Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in section II.D (1.5) above by providing the means for science- and risk-based decisions related to product quality.

Guidance for Industry
Q10 Pharmaceutical Quality System
April 2010

Operational Excellence

- Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

Guidance for Industry
Q10 Pharmaceutical Quality System
April 2010

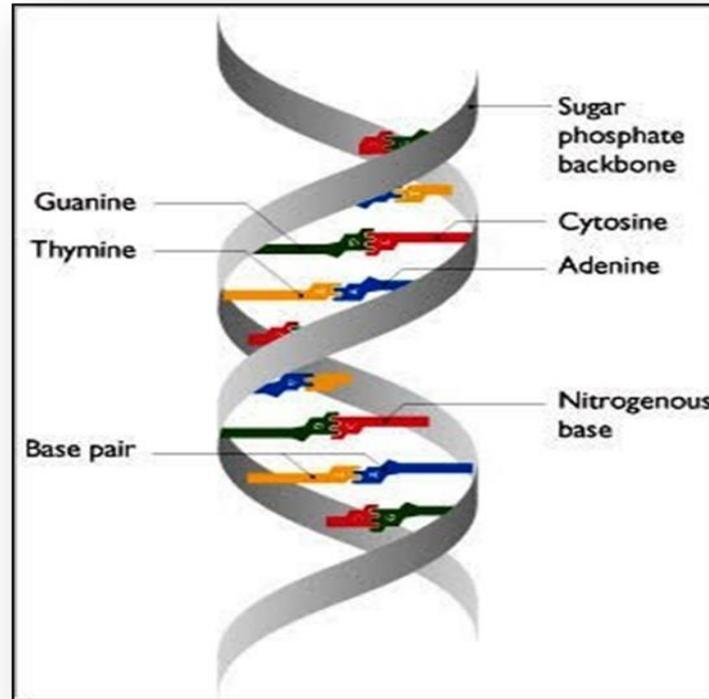
Quality Risk Management & Control Strategy

“This can include

- parameters and attributes related to drug substance and drug product materials and
- components, facility and equipment operating conditions,
- in-process controls, finished product specifications, and
- the associated methods and frequency of monitoring and control.
- The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action.”

Guidance for Industry
Q10 Pharmaceutical Quality System
April 2010

Operational Excellence



“Quality should be in our DNA”

Operational Excellence

I wonder if the aforementioned good thoughts are equally understood and embraced at the Shop-Floor level?

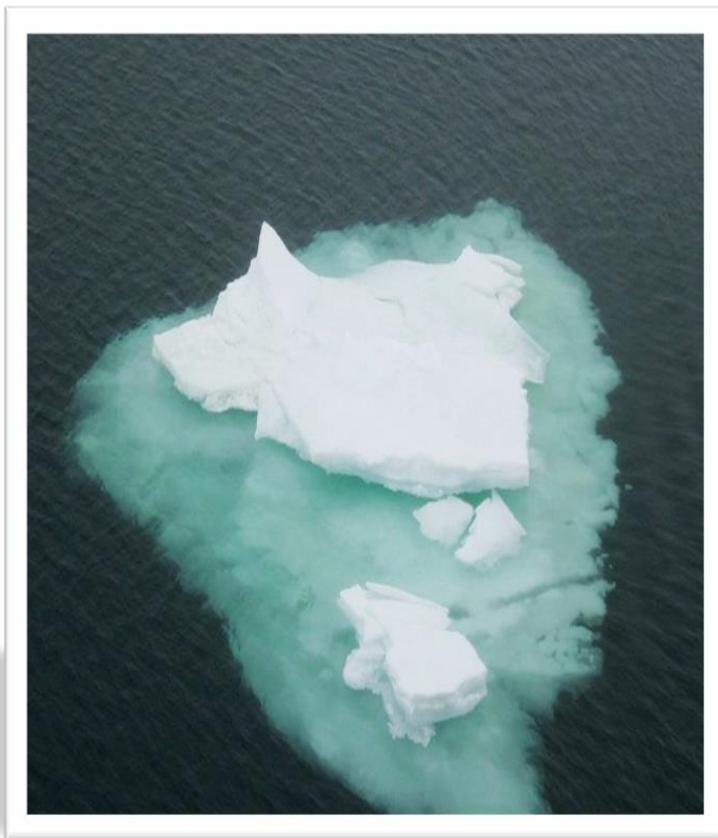


I believe we all agree with the good thoughts in Q10 and *“Quality should be in our DNA”*

- I will share with you that I am mindful of the following i.e., ...there is a *“general tendency of mankind to wishful thinking”* ...
 - Which, gets me to wonder that just maybe the understanding of the aforementioned concepts by personnel at the Shop-Floor is... *“wishful thinking”*

“Commentarii de Bello Gallico” (The Quest for Gaul, 58- 50 BC) – Julius Caesar

All that said and so you know...



- April 1991 - A highly respected FDA Investigator mentioned during routine inspections we (FDA) inspect about 5% of a manufacturing operations
- So then what is it that we (FDA) don't see that is below the water line and is the company aware of the other 95% that we may never see

Discussion



References and Acknowledgements

- Rick Friedman, CDER
- Thomas Arista, National Expert Pharmaceutical / Biotechnology
- CAPT Sharon Thoma, PharmD, National Expert, Pharmaceutical Inspections
- FDA Enforcement Statistics Summary
- Turbo EIR
- C.P. 7356.002 for Human Drug CGMP Inspections
- Title 21 CFR 210/211 (Drug GMPs)
- ICH Q9, Q10



Thank You!

Edmund F. Mrak Jr.
Drug Investigator
Pharmaceutical Inspectorate

US Food & Drug Administration
New England District

edmund.mrak@fda.hhs.gov
Office - 802-868-4725 x1104
Cell - 802-782-7239