Inspection Trends

American Society for Quality
Richmond, VA Section
March 8, 2016

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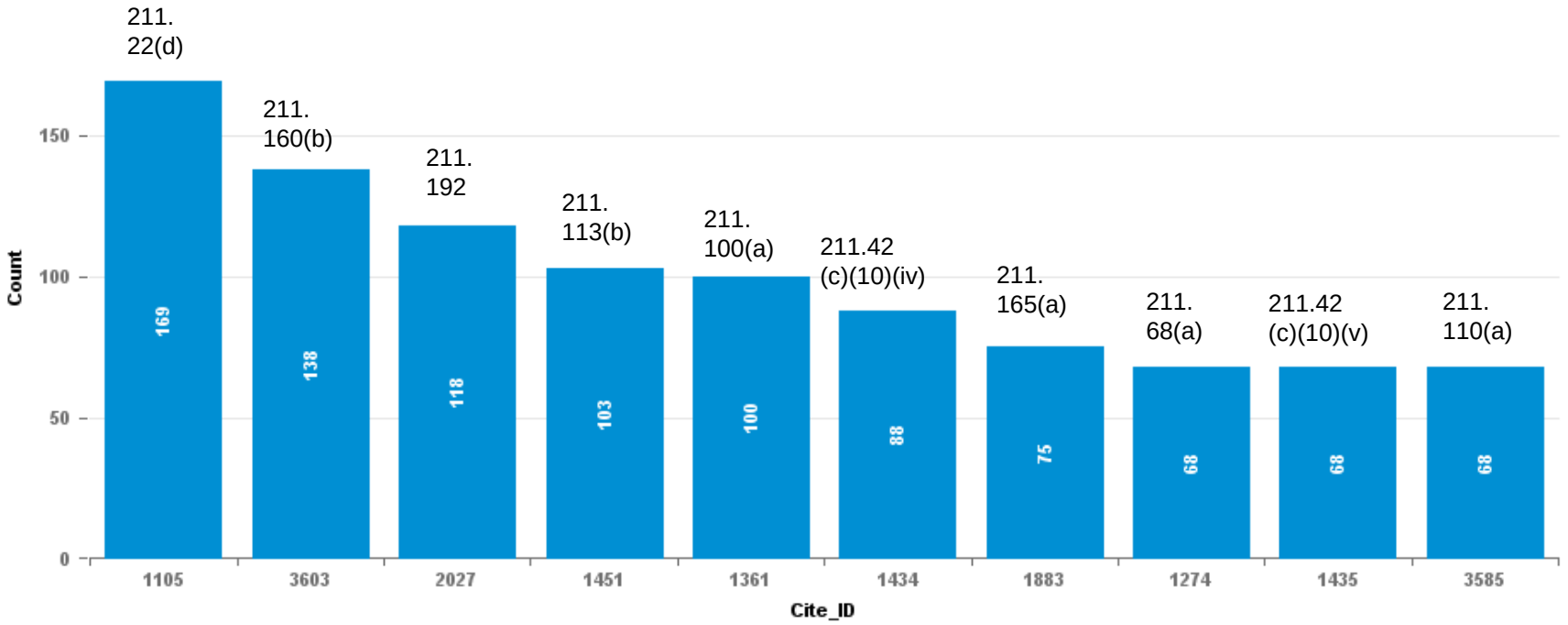
Agenda

- Inspectional Observation Trends
- Regulatory Action Trends
- Q&A Session

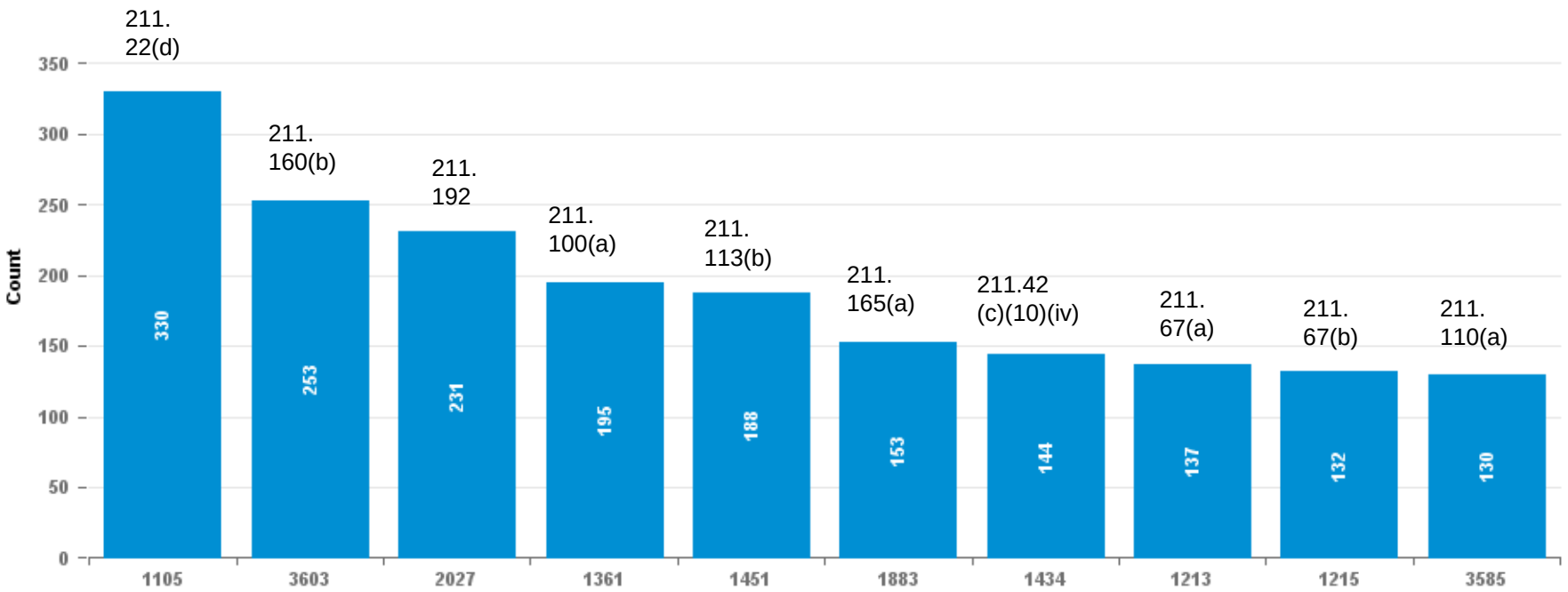
Inspectional Observation Trends

January 1, 2015 – January 1, 2016



Cite_ID	1105	3603	2027	1451	1361	1434	1883	1274	1435	3585
Count	159	138	118	103	100	88	75	68	68	68
Requirement	211.22(d)	211.160(b)	211.192	211.113(b)	211.100(a)	211.42(c)(10)(iv)	211.165(a)	211.68(a)	211.42(c)(10)(iv)	211.110(a)

January 1, 2014 – January 1, 2015



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Trend Evaluation (page 1)

- Eight of the top ten are the same cites
- 211.22(d): The responsibilities and procedures applicable to the quality control unit are not in writing or fully followed
- 211.160(b): Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures

Trend Evaluation (page 2)

- 211.192: Failure to thoroughly review any unexplained discrepancy or 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
- 211.113(b):Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written or followed.

Trend Evaluation (page 3)

- 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.
- 211.42(c)(10)(iv): Aseptic processing areas are deficient regarding the system for monitoring environmental conditions

Trend Evaluation (page 4)

- New to the list this year:
  - 211.68(a): Routine calibration, inspection and checking of automatic, mechanical and/or electronic equipment is not performed according to a written program designed to assure proper performance.
  - 211. 42(c)(10)(v): Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Inspection Trends

- What do they mean to FDA?
- What do they mean to you?

Investigations Operation Manual 5.2.3 – Reports of Observations

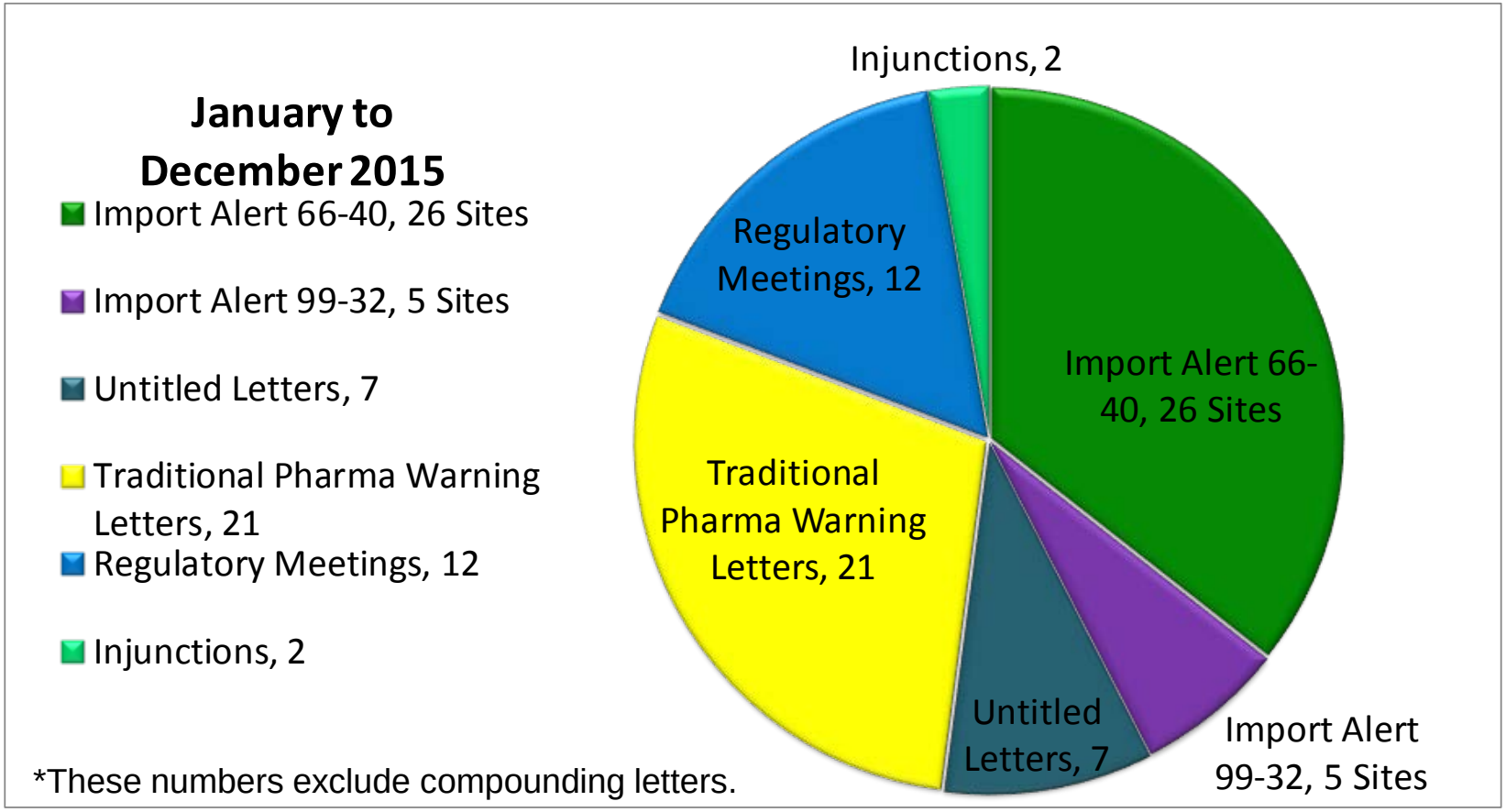
Observations are made when in the Investigator's "judgment", conditions or practices observed, indicate that any food, drug, device, or cosmetic have been adulterated or are being prepared, packed, or held under conditions whereby they may become adulterated or rendered injurious to health.

Inspectional Findings and Trends – Some Contributing Factors

- Regulatory maturity (regulators and inspected firms)
- Investigator background and expertise
- Company culture and management oversight
- Geographical location of inspected firms
  - Availability of required expertise

Regulatory Actions Trends

Compliance/OMQ Actions



*These numbers exclude compounding letters.

2015 Warning Letters

Manufacturer	Total	Import Alerts 66-40	Data Integrity Issues
API Manufacturer	12*	5	7*
Finished Pharmaceutical Manufacturer	13*	1	6*
TOTAL	21 LETTERS*	6 SITES**	13 SITES*

* Several sites manufacture both FDF and API.
**Import alerts issued in 2015 may correlate to Warning Letters issued in 2016

Note: Data integrity cited in 2015 warning letters

- It might seem that FDA takes issue with data integrity problems at overseas firms a disproportionate amount of the time. However:
  - ~80% of APIs are manufactured internationally
  - ~40% of FDFs are manufactured internationally
- Frequency of data integrity citations of overseas firms reflects that majority of APIs manufacturing is overseas.

What is Data Integrity?

Data integrity – requirements for complete, consistent, and accurate data.

The concept of data integrity underpins CGMPs.

Applies to CGMP and Good Clinical Practice (ICH E6).

Data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

ALCOA
Attributable
Legible
Contemporaneous
Original or true copy
Accurate

Parallel with Other Industries

Data integrity issues are not confined to the pharmaceutical industry!

- Enron
  - Much of the profits and revenue were result of deals with partnerships that it controlled.
    - Any debts or losses were not reported on financial statements
    - Offshore accounts hid the losses

Is this a new requirement? (page 1)

- 211.68 requires backup data are exact and complete, secure from alteration, inadvertent erasures, or loss
- 211.100 and 211.160 require certain activities be documented at the time of performance and that lab controls be scientifically sound
- 211.80 requires true copies or other accurate reproductions of the original records
- 211.188, 211.194, 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.
- 212.110(b) requires data be stored to prevent deterioration or loss

Is this a new requirement? (page 2)

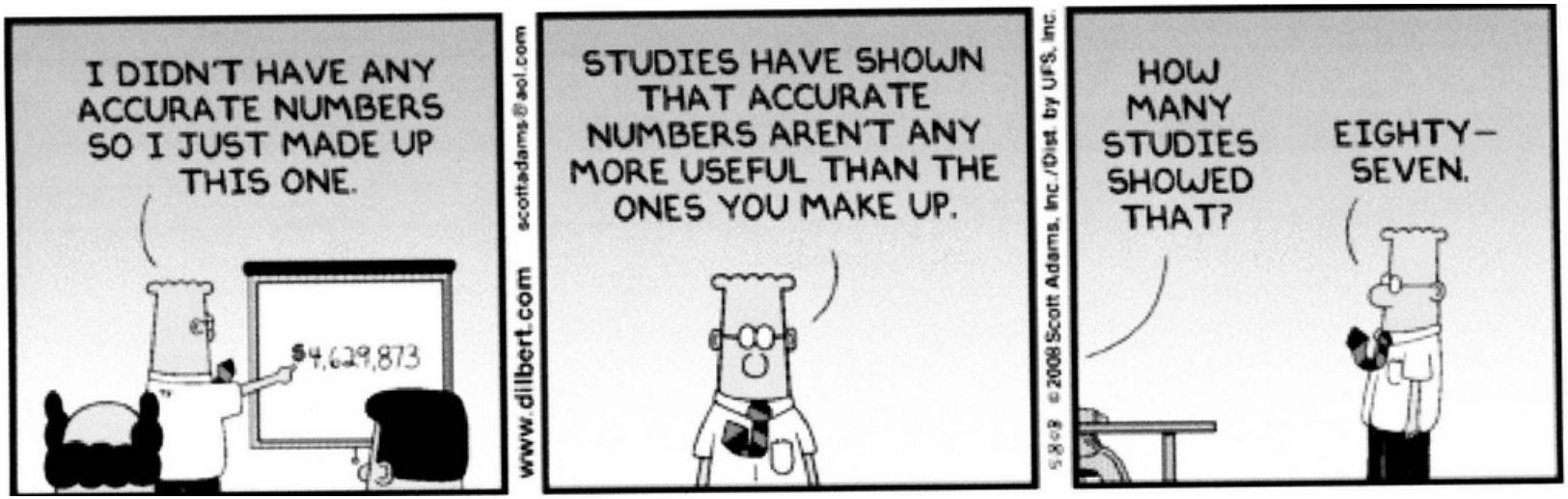
- APIs – ICH Q7: Computerized Systems (5.4)
  - Validation of GMP-related computerized systems; depth and scope depends on diversity, complexity, and criticality of computerized application
  - Is the software and hardware suitable to perform the task?
  - Record and investigate incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results.

Is this a new requirement? (page 3)

- APIs – ICH Q7: Computerized Systems (5.4)
  - Changes to computerized systems made according to change procedure; formally authorized, documented, and tested
  - Records of all changes, including modifications and enhancements to hardware, software, and any other critical component
  - Show the system is maintained in validated state.

Why is Data Integrity Important?

- We rely on accurate information to ensure drug quality
- Data integrity problems break trust
- We rely largely on trusting the firm to do the right thing when we are not there



Important Concepts

- Metadata
- Audit Trails
- Static versus dynamic records
- Backup datasets
- System validation

Important Concepts (continued)

- Metadata – describes attributes of other data, provides context and meaning
  - audit trails
  - Processing information, methods
- Static: Fixed Record, Print out
- Dynamic: Electronic record that the user can interact with
  - Smoke studies: Video versus photo
  - Chromatography: chromatogram versus online where you can see changes, reprocessing, baseline expansion
- Backup: editable data, including metadata, system configuration settings
- System validation: including backup and recovery process

FDA Authorities

CGMP mandated by the U.S. Food Drug and Cosmetic Act

> A drug…shall be **deemed to be adulterated**…if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, **and meets the quality and purity characteristics, which it purports or is represented to possess.** (Section 501(a)(2)(B) of the FD&C Act)

Finished pharmaceuticals must meet U.S Code of Federal Regulations – Title 21 CFR 210-211

Active Pharmaceutical Ingredients are subject to statutory CGMP requirements – Also refer to ICH Q7 Guideline

FDA Authorities (continued)

CGMP mandated by FD&C Act

- (501(a)(2)(B)) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B))
- http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm
- Finished pharmaceuticals must meet U.S Code of Federal Regulations – Title 21 CFR 210-211
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
- Active Pharmaceutical Ingredients must meet ICH Q7 Guideline links to PDF
- APIs are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the FD&C Act
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

2015 Warning Letters (page 1)

Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

- Trial HPLC, GC, and UV injections
- Raw data (sample preparation) not maintained
- Discarded data in the trash

2015 Warning Letters (page 2)

For related substances analysis, three sample injections of vial 1_8 named “TEST” were run prior to the reported sample injections. The “TEST” injection data was stored in the “Trial” folder located on a personal computer with no audit trail linked to the HPLC.

During the inspection, the calculations you performed using the target sample weight showed the “TEST” injections were OOS as compared to the specification. The “TEST” injections were not reviewed and evaluated when making the batch release decision.

2015 Warning Letters (page 3)

The official High Performance Liquid Chromatography (HPLC) impurity data for **(b)(4)** mg Tablets batch **(b)(4)**(**(b)(4)**), 3-month stability time-point @ 25°C/60% RH only included the most favorable result obtained from multiple test results without any justification. The data from this batch was submitted to the U.S. FDA as an exhibit batch.

2015 Warning Letters (page 4)

Your firm failed 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 (21 CFR 211.68(b)).

- Lack of basic lab controls to prevent changes to electronically stored data
  - Audit trails turned off
  - No controls to prevent substitution, deletion, or overwriting of data
  - Sharing user names and passwords

2015 Warning Letters (page 5)

QC personnel created unauthorized folders on lab computers without appropriate oversight. Our review of HPLC Empower III data collected in 2013-2014 found a data folder entitled “WASH.” According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no SOP detailing this process. One of your lab analysts stated this folder does not contain any standard or sample injection results. However, our investigator found this folder contained a total of 3,353 injection results, some of which appeared to be samples.

2015 Warning Letters (page 6)

Ten Shimadzu HPLC instruments in the QC "commercial" lab were configured to send acquired injection data to PCs without audit trails.

2015 Warning Letters (page 7)

Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

- The inspection found the audit trail feature for your gas chromatography instruments was not used until October 2013, even though your 2009 GC software validation included a satisfactory evaluation of the audit trail capability.

2015 Warning Letters (page 8)

Failure to record activities at the time they are performed and destruction of original records.

- “Rough notes” (unbound, uncontrolled loose paper) used to capture original critical manufacturing data were destroyed after transcription into the batch production records.
- Backdating of production records when personnel were not onsite to perform the activity

Summary

Data integrity breaches:

- Undermine assurance of pharmaceutical quality (and potentially safety and efficacy)
- Break down basic trust with regulator and public
- **Are a fundamental failure of the Quality System**

Q&As on Data Integrity

Are shared login accounts OK for computer systems?

Are electronic signatures OK for master production and control records?

Can we use actual samples to perform system suitability testing?

Detailed discussion online:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm

2016 CDER Guidance Agenda includes CGMP Data Integrity Questions and Answers

New Q&As (Level 2 Guidance)

- New Q&As (Level 2 Guidance) addressing Data Integrity were published online in August 2014.
- Address common recurring issues we're finding in inspection reports.
- Are shared login accounts OK for computer systems? No
- Are electronic signatures OK for master production and control records? Yes
- Can we use actual samples to perform system suitability testing? No. We discourage testing into compliance.
- URL for new Q&As: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm
- URL for 2016 CDER Guidance Agenda: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417290.pdf

References

FDA's Electronic Reading Room – Warning Letters:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

FDA compliance information online:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm

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