FDA U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF GLOBAL REGULATORY OPERATIONS & POLICY
OFFICE OF INTERNATIONAL PROGRAMS

Data Quality and Integrity Investigation in Laboratories (Analytical)

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Disclaimer

The views and opinions expressed in this presentation are those of the author and do not necessarily represent the official policy or position of the U.S Food and Drug Administration

Data Quality & Data Integrity

- **Data Quality**: The completeness, accuracy, timeliness and consistency of stored information
- **Data Integrity**: The completeness, accuracy, and consistency of data
- Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)

- Data quality drives data integrity

Data Integrity and Compliance With CGMP

FDA Data Integrity Requirements

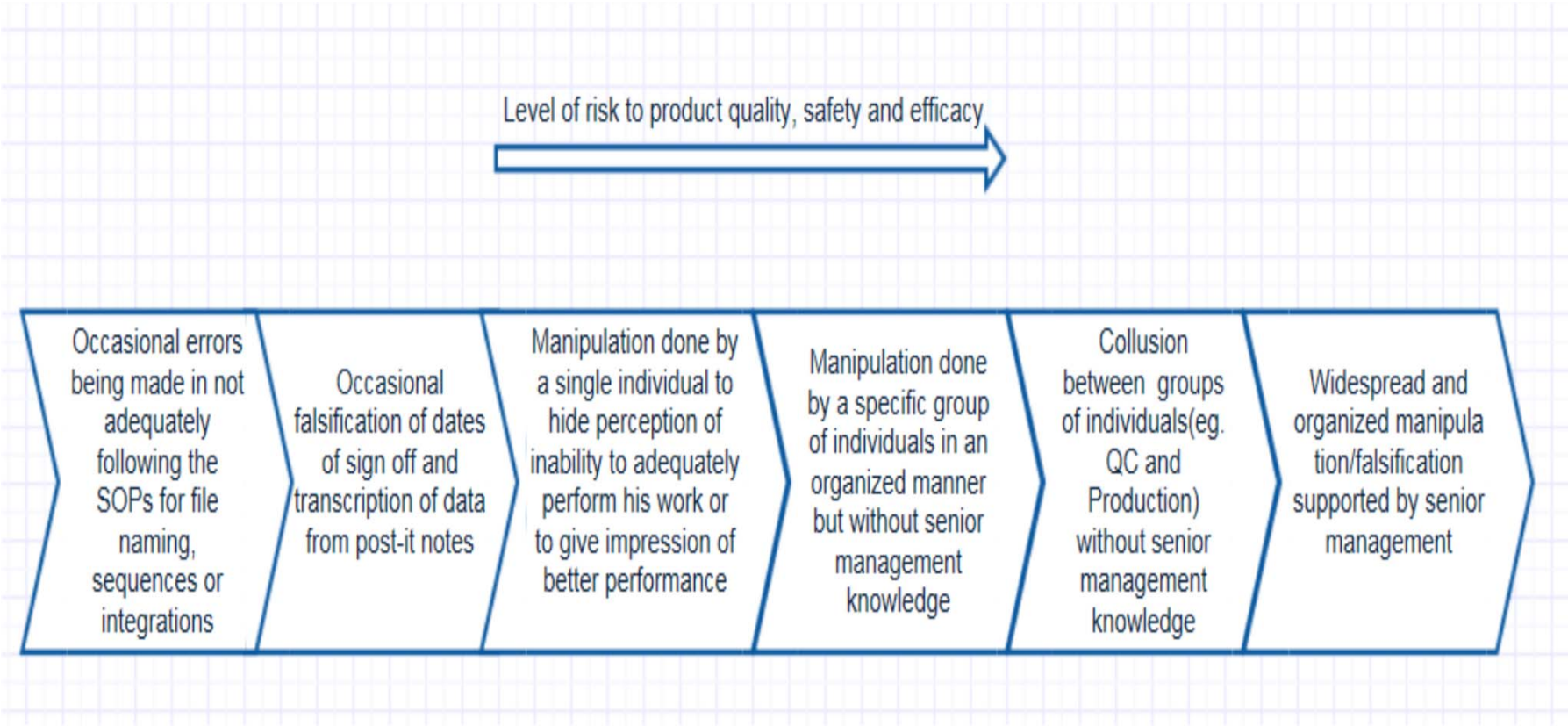
Include…

- 211.68 (“backup data are exact and complete,” and “secure from alteration, inadvertent erasures, or loss”);
- 212.110(b) (data is “stored to prevent deterioration or loss”);
- 211.100 and 211.160 (activities be “documented at the time of performance” and laboratory controls be “scientifically sound”);
- 211.180 (records be retained as “original records,” “true copies,” or other “accurate reproductions of the original records”);
- 211.188, 211.194, and 212.60(g) (“complete information,” “complete data derived from all tests,” “complete record of all data,” and “complete records of all tests performed”).

Why Data Integrity Issues are Mostly Found in the Lab

- Data integrity problems do not apply only to QC, but the QC lab is where many symptoms of data integrity problems and GMP/Quality problems will be seen.
- E.g., if a company is having problems in sourcing good quality starting materials and producing good quality products, this is likely to be visible in the QC laboratory's test results.

The "Spectrum" of Data Integrity Issues



If The Laboratory is a Gold Mine!

Electronic software and OOS Investigations Are Treasure Chests!

Electronic Systems

Common data integrity issues encountered during review of electronic laboratory data (HPLC/GC/UV/FT-IR/Karl Fischer/Particle Counts)

1. Trial Sample Analysis
2. Deletion/Overwrite of Data
3. Testing Into Compliance
4. Back-door Manipulation
5. Administrator Foul Play
6. Physical manipulation
7. Extraneous peaks not processed
8. Manual reintegration

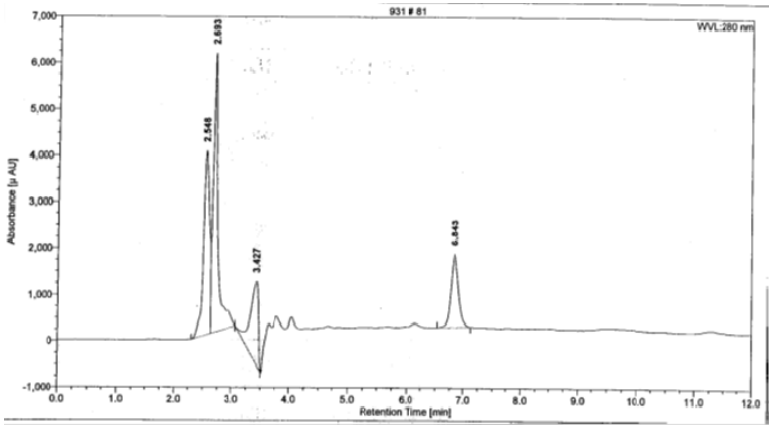
Trial Sample Analysis

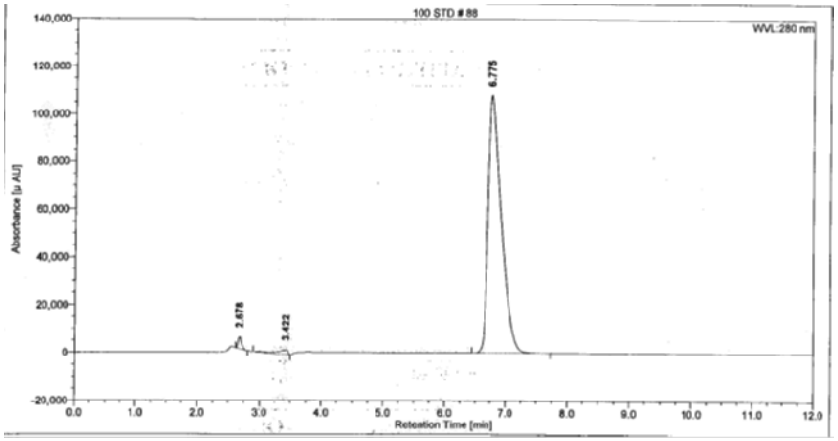
Prior to testing the 'official' samples, trial samples are pre-tested to determine if they will meet specifications

- Results are not documented and investigated according to written procedures
- Results often differ from the subsequent official analysis (e.g. fail specifications)
- Suggests that the analyst is choosing only those sample solutions found to be meeting specifications
- They are vaguely identified e.g. test, trial, SS

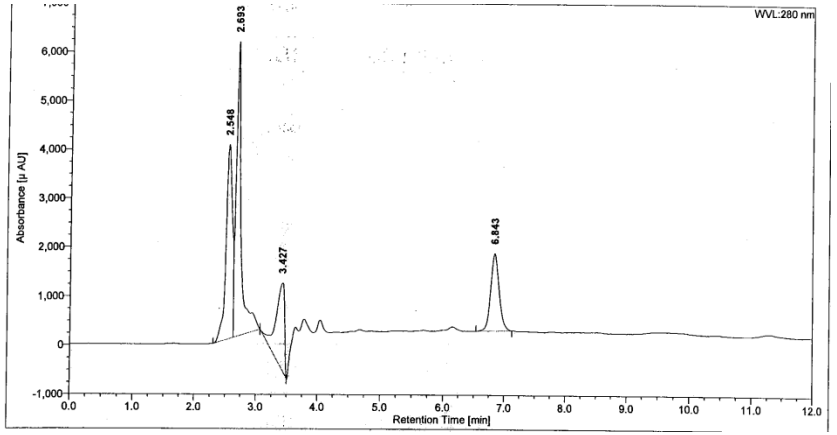
Trial Sample: Sample or Standard?

Trial Injection





www.fda.gov Official Standard Injection



Official Sample Injection – 4 hour Acid

Trial Sample Analysis

- 4 – hour acid dissolution specification = NLT 60%

Trial

Name	Vial Position	Peak Area	Area Similarity	% Dissolution	Meets Specification
Disso 1	101	111,312	Acid (4 hours)	65%	Yes
Disso 2	102	120,561	Acid (4 hours)	70%	Yes
Disso 3	103	115,984	Acid (4 hours)	68%	Yes
Disso 4	104	60,837	Acid (4 hours)	30%	**No**
Disso 5	105	110,512	Acid (4 hours)	64%	Yes
Disso 6	106	65,943	Acid (4 hours)	33%	**No**

Official

Name	Vial Position	Peak Area	% Dissolution	Meets Specification
B0654 Acid 4 hours – 1	101	111,453	65%	Yes
B0654 Acid 4 hours – 2	102	120,123	70%	Yes
B0654 Acid 4 hours – 3	103	115,894	68%	Yes
B0654 Acid 4 hours – 4	**104**	**115,548**	**68%**	**Yes**
B0654 Acid 4 hours – 5	105	110,185	64%	Yes
B0654 Acid 4 hours – 6	**106**	**110,631**	**64%**	**Yes**

Deletion of Data

- Individual files or folders could be deleted within the analytical software.

  - Software that allows the user to view the results, but does not require saving of data.

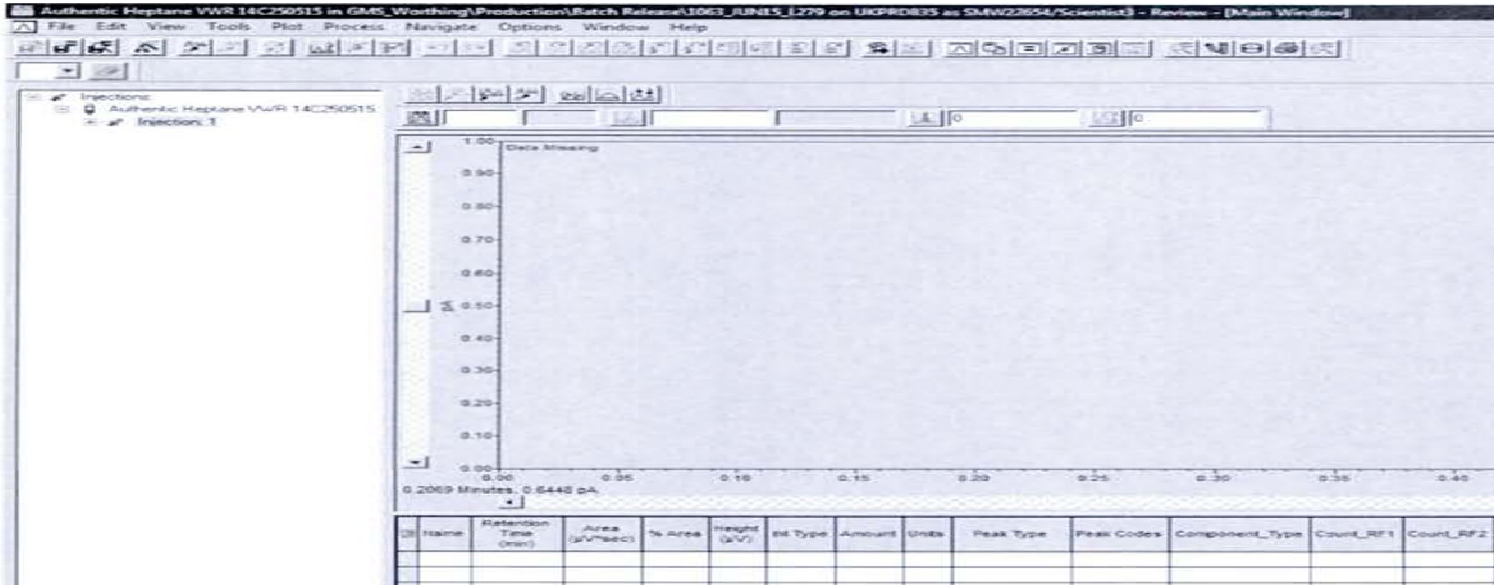
- Source data is deletable from the hard drive of the associated computer.

Overwriting of Data

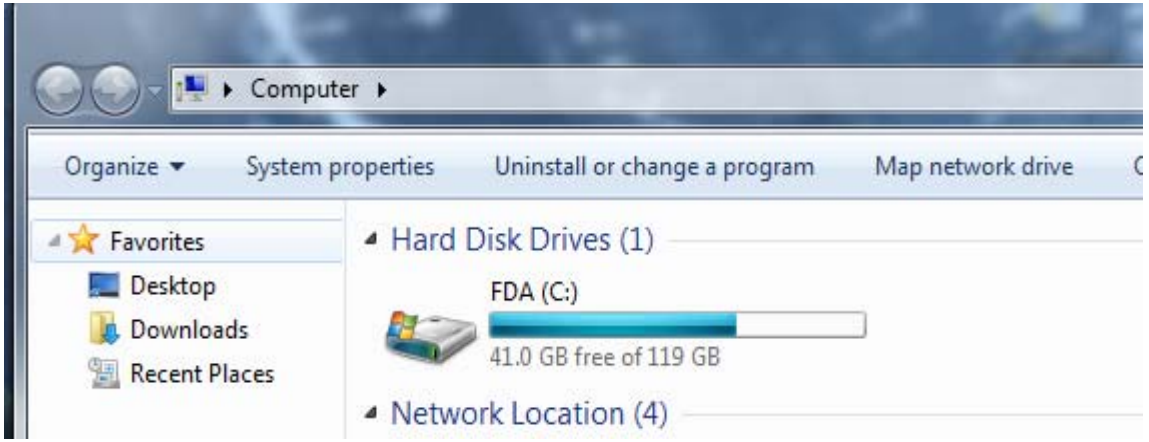
Steve	1/29/2013 15:19	Sequence - Acquire and Analyze Run 4 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\004.dat
Steve	1/29/2013 14:43	Sequence - Acquire and Analyze Run 3 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\003.dat
Steve	1/29/2013 14:07	Sequence - Acquire and Analyze Run 2 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\002.dat
Steve	1/29/2013 13:05	Sequence - Acquire and Analyze Run 1 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\001.dat

Steve	1/29/2013 19:08	Sequence - Acquire and Analyze Run 4 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\004.dat
Steve	1/29/2013 18:33	Sequence - Acquire and Analyze Run 3 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\003.dat
Steve	1/29/2013 17:57	Sequence - Acquire and Analyze Run 2 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\002.dat
Steve	1/29/2013 17:01	Sequence - Acquire and Analyze Run 1 - D:\DATA\2013\Finish Product\Ibuprofen\29012013\001.dat

Deletion of Data



Injection is listed in the audit trail, but it is missing when we try to open it.



Back-ended deletion done through Windows.

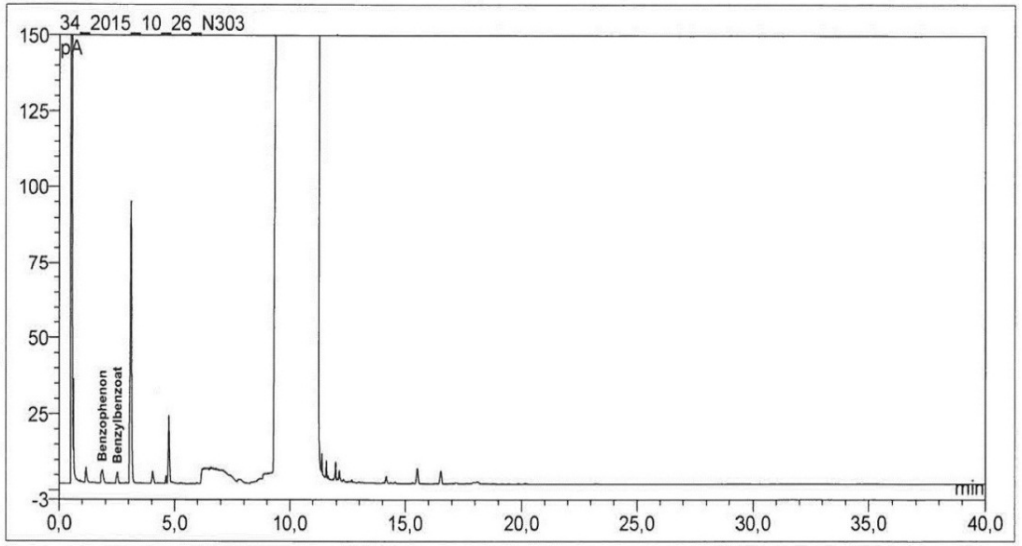
Testing into Compliance

- When undesirable results are encountered, samples are retested until acceptable results are achieved
  - No Laboratory OOS Investigation is initiated
  - Raw data may be destroyed
  - Electronic data may be deleted

Testing into Compliance

- The 1st injection was 10/30/15 at 11:23
- Specification for Benzophenone is <200ppm
- Injection fails at 238 ppm

Operator:	UIBBP	*Path:*	QC\GC\QGC_34
Vial Number:	81	*Injection Volume:*	1,0
Control Program:	AGC16010240	*Sample Type:*	unknown
Quantif. Method:	Benzophenon	*Run Time (min):*	40,00
Recording Time:	30.10.2015 11:23	*Column Info:*	10300849
Sample Weight:	0,1047		0,9011

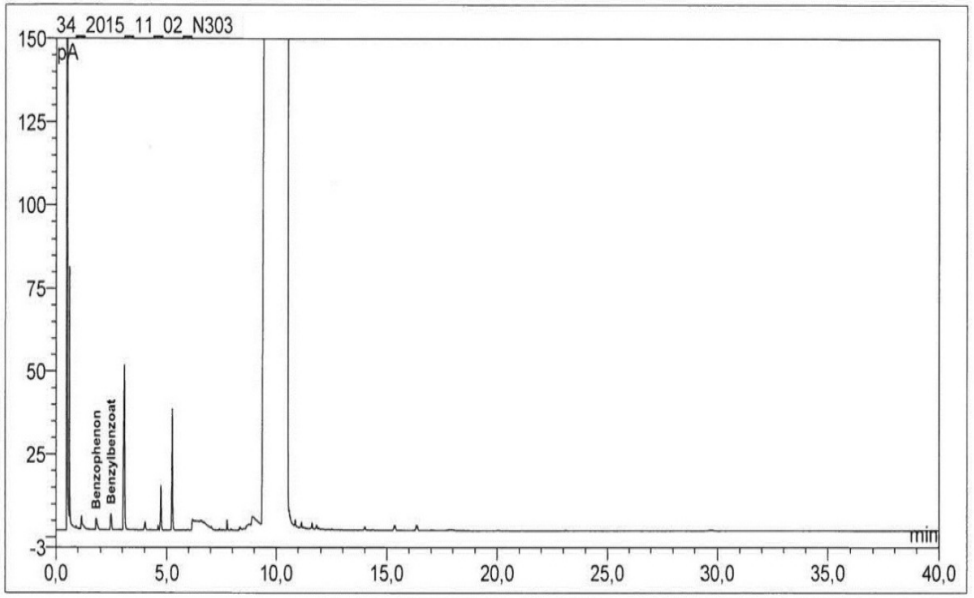


No.	Ret.Time min	Ret.Index	Area pA*min	Type	Area %	Amount ppm	Peak Name
5	1,861	1077,6	0,458	BMB	0,010	237,6995	Benzophenon
7	2,520	1242,1	0,291	BMB	0,006	200,2444	Benzylbenzoat
Total:			0,748		0,016		

Testing into Compliance

- The second injection was 11/3/15 at 21:32
- This injection passes at 117ppm
- This is the only reported data

Operator:	UIBBP	*Path:*	QC\GC\QGC_34
Vial Number:	84	*Injection Volume:*	1,0
Control Program:	AGC16010240	*Sample Type:*	unknown
Quantif. Method:	Benzophenon	*Run Time (min):*	40,00
Recording Time:	3.11.2015 21:32	*Column Info:*	10300849
Sample Weight:	0,1046		0,9125



No.	Ret.Time min	Ret.Index	Area pA*min	Type	Area %	Amount ppm	Peak Name
4	1,811	1049,9	0,240	BMB	0,013	117,2992	Benzophenon
6	2,495	1245,6	0,313	BMB	0,017	202,7778	Benzylbenzoat
Total:			0,552		0,030		

Electronic Data Reprocessing

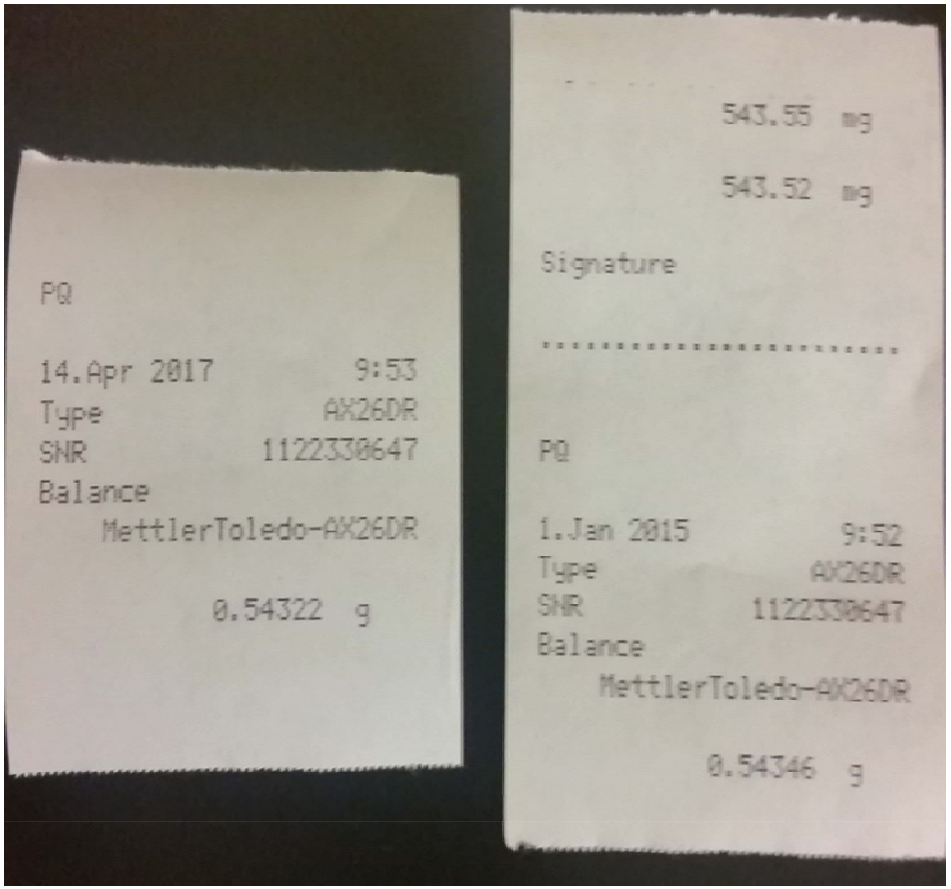
- **Reprocessing should not be regularly needed if** analytical methods are capable and stable.
- If chromatography is reprocessed, written procedures must be established and followed and each result (original + reprocessed) retained for review .
- **It is NOT acceptable to only save the final results from reprocessed laboratory chromatography**

Is it Permissible to Exclude CGMP Data From Decision Making?

- To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion.
- Record retention and review requirements are the same for paper-based and electronic data
- All records required under CGMP are subject to FDA inspection.

Back-door Manipulation

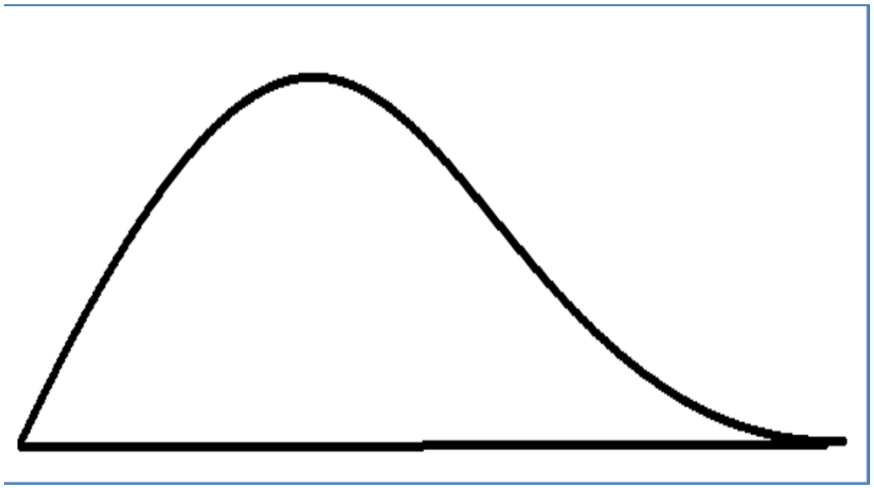
- Changing the sample weight
  - Altering the sample weight for an Assay analysis to increase or decrease potency as desired.

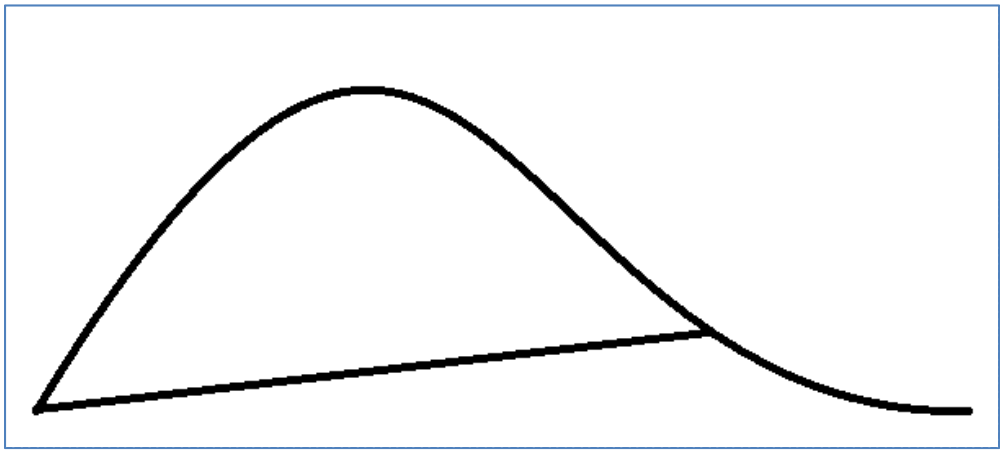


Back-door Manipulation

Integrating into compliance

- Increasing or decreasing peak cut-off points to achieve passing results.
- Using integration parameters to suppress valid peaks
- etc





Administrator Foul Play

- Using Administrator privileges to turn off/on audit trails - hide trial analyses or data manipulation
- Using Administrator Privileges to set the controlling PC clock back in time - repeat failing runs

Number	Action	Details	Change Date	User
8134	Altered System Policy	Change time and date settings Reason: ok	2014/7/25 AM 10:16:47 Asia/	900161/Administrator
8135	Altered System Policy	Change time and date settings Reason: ok	2014/7/21 AM 10:00:00 Asia/	900161/Administrator
8329	Altered System Policy	Full Project Audit Trail - Not Active --> Active Reason: ok	2014/7/20 PM 04:15:09 Asia/	900161/Administrator
8350	Altered System Policy	Full Project Audit Trail - Active --> Not Active Reason: ok	2014/7/20 PM 03:43:50 Asia/	900161/Administrator
19034	Altered System Policy	Applications Timeout Time - 60 minutes --> 5 Reason: no	2013/9/4 AM 10:41:42 Asia/	900161/Administrator
19035	Altered System Policy	Applications Timeout Time - 3 minutes --> 60 Reason: no	2013/9/4 AM 10:41:13 Asia/	900161/Administrator
25966	Altered System Policy	Full Project Audit Trail - Not Active --> Active Reason: ok	2012/12/6 AM 08:33:45 Asia/	900161/Administrator
26272	Altered System Policy	Full Project Audit Trail - Active --> Not Active Reason: ok	2012/12/5 AM 10:01:44 Asia/	900161/Administrator
26273	Altered System Policy	Enforce Sign-Off Inactivity - True --> False Reason: add setting "time out"	2012/12/5 AM 10:01:44 Asia/	900161/Administrator
26297	Altered System Policy	Sign-Off Inactivity Delay - 10 minutes --> 5 Reason: add sing off inactivity delay time	2012/12/4 PM 01:35:34 Asia/	900161/Administrator
26298	Altered System Policy	Enforce Sign-Off Inactivity - False --> True Reason: add sing off inactivity delay time	2012/12/4 PM 01:35:34 Asia/	900161/Administrator

Physical Manipulation

Equipment physically manipulated:

- Forcing the equipment to fail to provide a reason for invalidation of already generated data.

- Preventing the equipment from transferring or saving the data…cable disconnect.

Honorable Mention

- Sharing user names and passwords
- Backdating of analyses, such as stability tests, in order to meet the required commitments
- Reuse of old data, passing it as new data, to avoid performing supplementary analyses (saving time and money…?)
- Failure to record activities at the time they are performed
- Creation of false records during an inspection
- **Leaving out systems that are labeled “R&D systems" from the inspection.**

OOS Investigations

What is a meaningful OOS investigation?

- Thorough
- Timely
- Unbiased
- Well-documented
- Scientifically sound

OOS Investigations and Data Integrity

1. **Invalidating out-of-specification test results**

   Disregarding OOS results without scientific justification

2. **Testing Into Compliance**

   Repeated testing until a passing result is obtained

3. Inserting failed system suitability standards in a sequence
4. Finding a flaw in the analysis after the fact
5. Failure to extend investigation to other batches
6. Averaging of failed replicates
7. Sample weight manipulation

Testing Into Compliance

- **Testing Into Compliance**
  - **Repeated testing** until a passing result is obtained
  - **Disregarding** OOS results without scientific justification

- **Retesting**
  - **Maximum number** of retests NOT specified in SOP
  - May vary based on **variability of method**
  - IS adjusted during OOS Investigation
  - Testing NEVER seems to **end** and batch NOT evaluated

Averaging of OOS Results

- **Averaging**
- **Inappropriate Use**
  - Blend Uniformity
  - Content Uniformity
  - **Averaging OOS** results with **in-spec** results to obtain a **passing result**
  - Averaging **in-spec testing results** obtained during an **OOS investigation** with the **original OOS results to obtain passing result**

Averaging of OOS Results

- What if there is **no valid reason** to invalidate the original OOS results?
- **What should the firm do?**
- Keep **all** the results
- Do **NOT** average **ANY** of the results
- Evaluate **all** the **individual** results against the **written specifications**

Averaging of OOS Results

- Specification equals 90.0 – 110.0 %
- Example 1:
  - 90.0, **89.9**, 90.1, 90.3, 90.0, 90.2, 90.0, 90.0
- Example 2:
  - **89.9**, 99.2, 98.7, 99.3, 99.1, 99.4, 98.9, 99.0

Failure to Extend Investigation

- So the OOS result is confirmed and the root cause identified. The firm closes the investigation and rejects the product. Time to move on. Right?
- **Not so fast!**
- A failure investigation that extends to other batches or products that may have been associated with the specific failure must be completed.
- (**21 CFR § 211.192**)

- Why is this a common violation?

More Reasons For 21 CFR 211.192 Violations

- Difficult and time-consuming to investigate related batches
- Shutdown Production
- What about the batches on the market?
- It becomes a wrestling match between

- **Quality Control Unit** & Pharma Mgmt

And Even More Reasons For 21 CFR 211.192 Violations

- OOS results may indicate a flaw in product/process:
  - A lack of robustness in product formulation
  - Inadequate raw material characterization or control
- If so, what now???
  - Redesign of the product/process
  - FDA Approval Process again
- How many firms want to do that?

Concluding The OOS Investigation: Caution

- Individual results of a test should be expected to produce a result that meets specification

- If assay is low, but within specification, it may suggest that batch was not formulated properly.
  - 21 CFR § 211.101 (a) – Firm Investigate?

- 21 CFR § 211.194 - **Records** must be kept of **complete data** derived from all tests performed to ensure compliance with established specifications and standards.

Data Quality and Integrity Investigations - *Triggers*

- Too good to be true
- Internal audit
- Audit trails
- Reprocessing - How often??
- Missing HPLC/GC vials ??
- Expired samples – deliberate delays???
- Failed system suit…how often?
- Failed bracketing standard spec??
- List of OOS Investigations
- Firm's SOP for OOS vs. FDA Guidance
- Analyst error ??? How Often?
- Instrument Error
- Unknown? What now?
- Averaging OOS – NEVER!
- Testing Into Compliance
  - Everyone Else Does It!

Addressing Lab Data Integrity

- Determine the scope of the problem
- Demonstrate effective remediation of problems
  Third party auditor
- Implement a corrective action plan (globally),
- Remove at all levels individuals responsible for problems from CGMP positions.

Scope of DQ & I Investigations

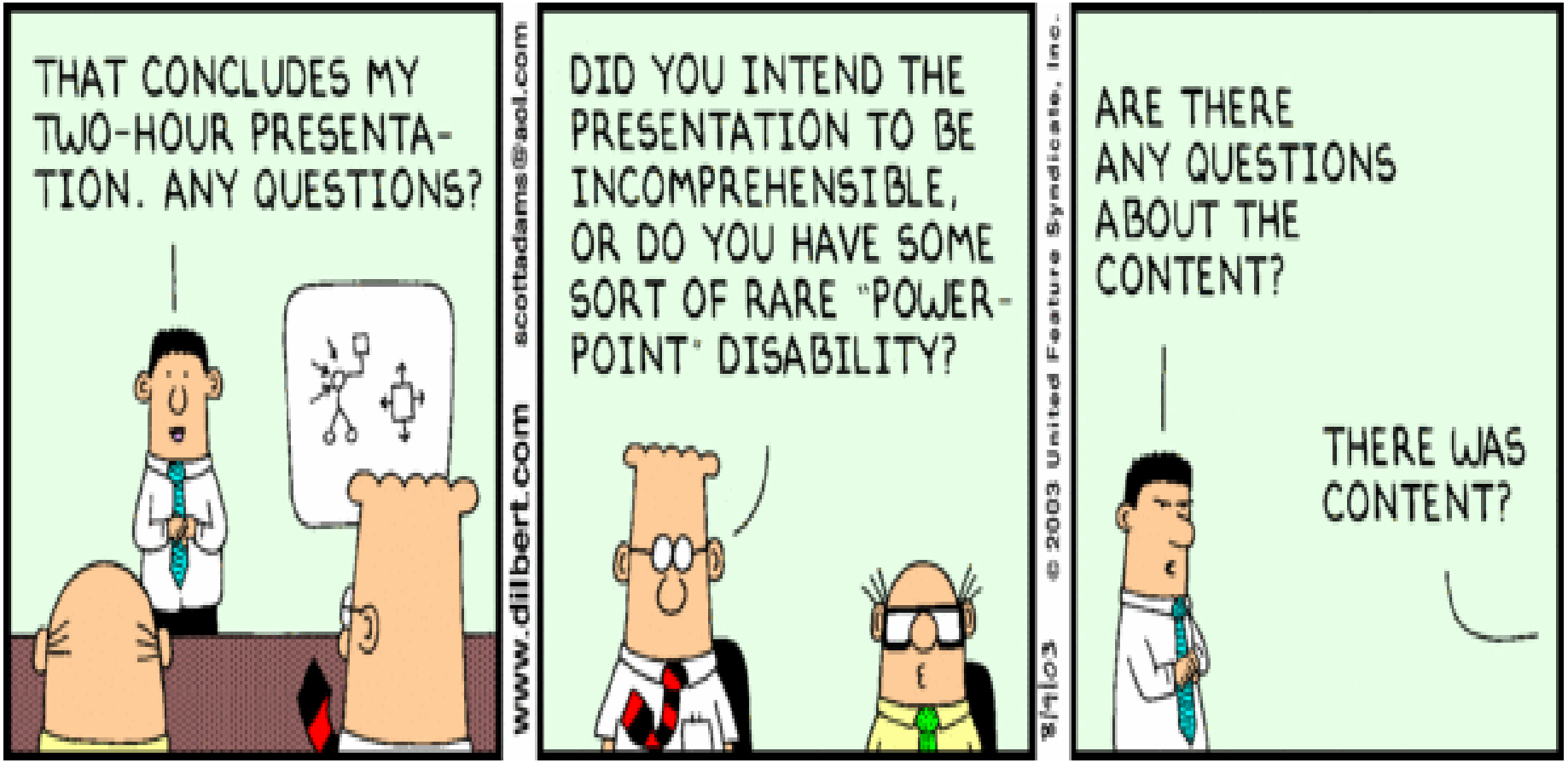
- Suspected or known falsification or alteration of records required under parts 211 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken.

Review of Audit Trails

- Audit trail review is critical both to the detection and correction of electronic data integrity problems.
- Audit trails must be reviewed with each record and before final approval of the record.
- Review should include, but are not limited to: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters.
- Must be reviewed and approved by the quality unit

Prevent & Deter, The Best Policy

- **Prevent:** Personnel **MUST BE** trained in detecting data integrity issues as part of a routine CGMP training program
- **Deter**: A comprehensive ethics program that describes standards for employees and procedures for educating employees about data integrity implications and for enforcing a **zero tolerance policy** within quality control laboratories
- Independent System Administrator, not QC Manager!


THAT CONCLUDES MY TWO-HOUR PRESENTATION. ANY QUESTIONS?
www.dilbert.com scottadams@aol.com
DID YOU INTEND THE PRESENTATION TO BE INCOMPREHENSIBLE, OR DO YOU HAVE SOME SORT OF RARE "POWERPOINT" DISABILITY?
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8/4/03
ARE THERE ANY QUESTIONS ABOUT THE CONTENT?
THERE WAS CONTENT?

References

- Guidance for Industry Draft Guidance: Data integrity and compliance with cGMP (April 2016)
- Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006)
- Boyd, J. (2017): Data integrity in quality control: Inspector perspective
- Panagiotis, S. (2014): OOS Investigations
- Croft, S. (2013) Quickest ways to find data integrity issues during inspections

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