Dangerous Data

How to Rapidly Assess for Data Integrity Issues

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Could you imagine the head of quality at at firm saying to an FDA investigator:

___ 1. "We don't commit fraud – we don't rely on formal written contracts; you need to trust us as we trust our people and suppliers."

___ 2. "We outsource the data integrity function so it's the responsibility of our contractor to ensure the integrity of our data."

____ 3. "We don't worry about data integrity issues, our IT department backs everything up."

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The mine could explode ….

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Agenda

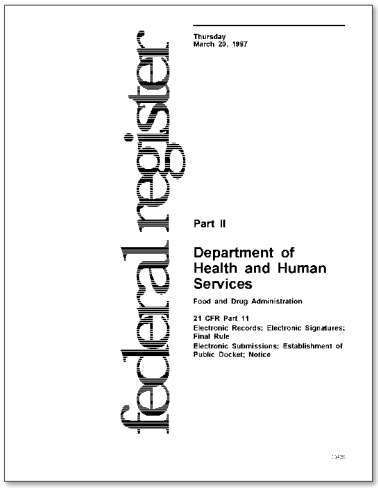
- How data integrity became an issue
- Ignorance/negligence/fraud
- Three rapid red flag questions
- Warning signs that you can find in audit trails in 300 seconds or less
- Six key records to request

Generic Drug Scandal

- 1989
  - 9 companies were investigated for falsifying drug records for new generic drugs
  - Using computers, they **copied electronic test results** for brand drugs
  - Then they claimed these, as the testing results for new generics
- 1993
  - 30 individuals convicted of fraud
  - Former CEO of Bolar Pharmaceuticals
    - Received $10M fine
    - 5 years in prison

Electronic Records; Electronic Signatures

- Issue was discussed in early 1990s
- 1997 published as a final reg, 21 CFR 11
- Established conditions
  - Under which FDA would consider e-records (and signatures)
  - To be the equivalent of paper records and pen/ink signatures
- Applies to **all records** (and signatures)
  - Required under any FDA regulation and
  - Kept or used in digital form


Thursday
March 29, 1997

federal register

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 11
Electronic Records; Electronic Signatures; Final Rule
Electronic Submissions; Establishment of Public Docket; Notice

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"For **electronic records** to have the **same integrity** as paper records, they must be developed, maintained, and used under **controls** that make it difficult for them to be inappropriately modified."

- Steve Wilson, Deputy Director, FDA CDER, May 2006

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"One out of every 50 scientists today **falsify data**."

- Daniele Fanelli, Stanford University, "How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data," *PLOS One*, May 2009

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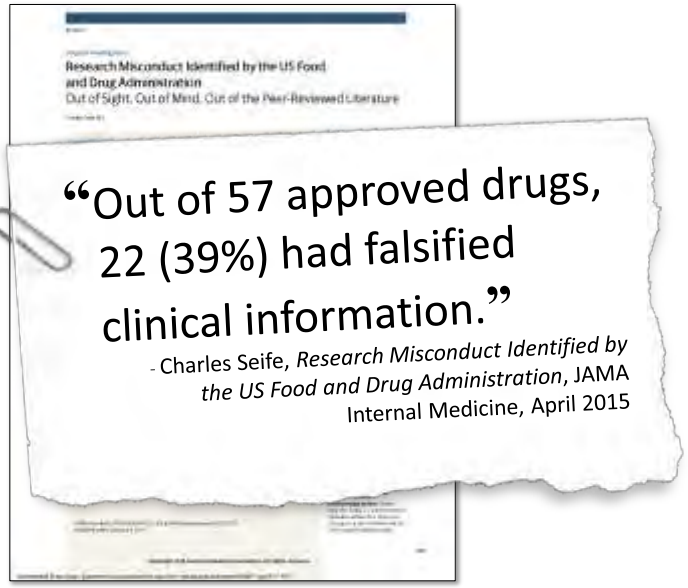

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Question for the Government -

Which data

Can't we trust?

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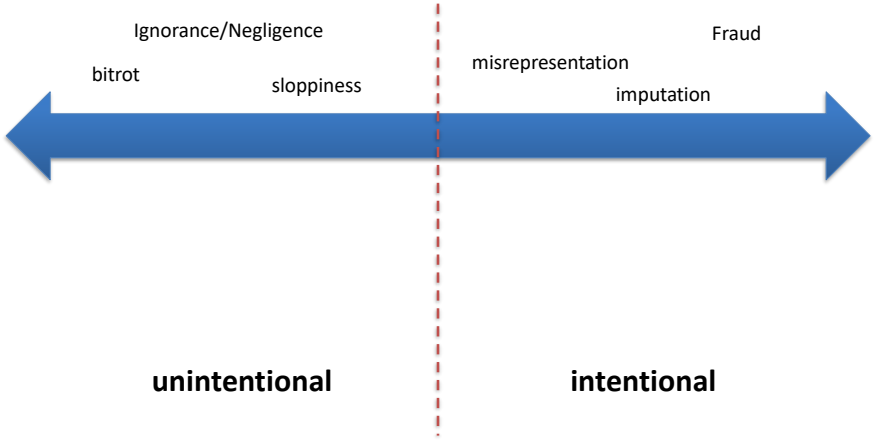
Put Lack of Data Integrity on a Continuum



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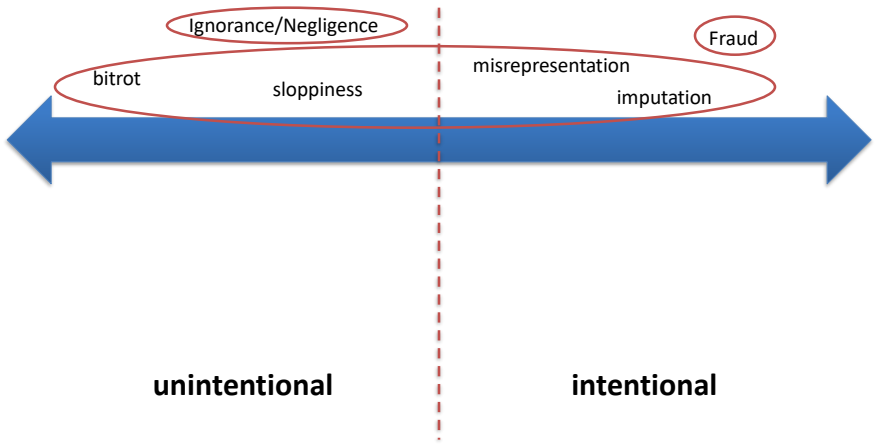
How Should FDA Prioritize Its Activities around Data Integrity?



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Ideas to Consider

- For firms who commit fraud, FDA needs to –
  - Institute criminal prosecutions,
  - Levy monetary penalties, or
  - Recommend they be placed on AIP
- For firms who are negligent and/or ignorant, FDA needs to
  - Cite them in 483 observations and
  - Send them warning letters
- The Challenge is that most of the industry falls into the negligent/ignorant category.
- FDA needs to prioritize its activities.

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Which is Worse?

a) The sponsor firm has no data integrity controls to prevent, catch, or mitigate data fraud and data loss.

b) The sponsor firm has data integrity controls to prevent, catch, or mitigate data fraud and data loss, but doesn't consistently follow their own controls.

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When FDA prioritizes its activities, which should they spend time inspecting?

A. Sponsors

B. Investigators

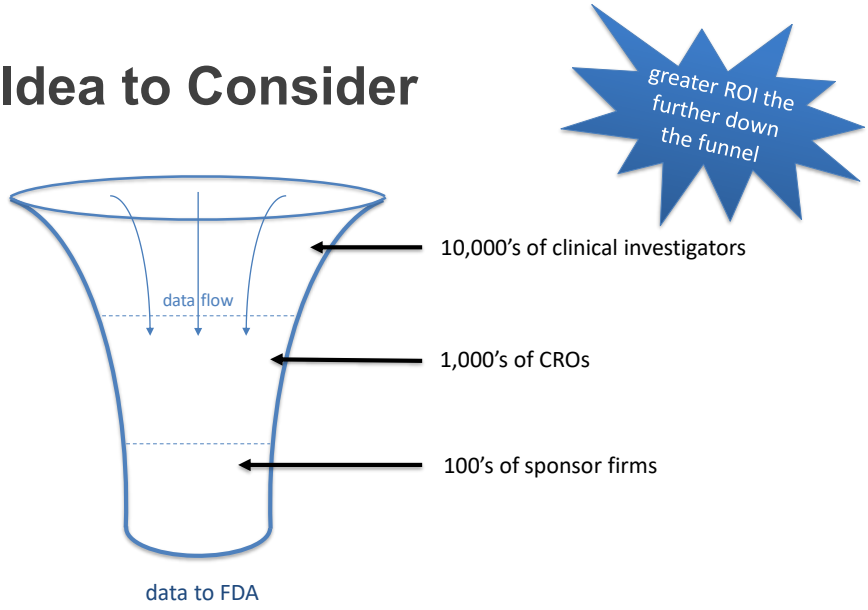
A. Contract Research Organizations (CROs)

Our Suggested Answer

A. Sponsors

- When criminally prosecuting a company, the FDA takes action against the president who has the responsibility and authority to ensure that the company complies with regulatory requirements.
- Under the same principle, the sponsor has authority and responsibility to see that its clinical investigators comply with the law.

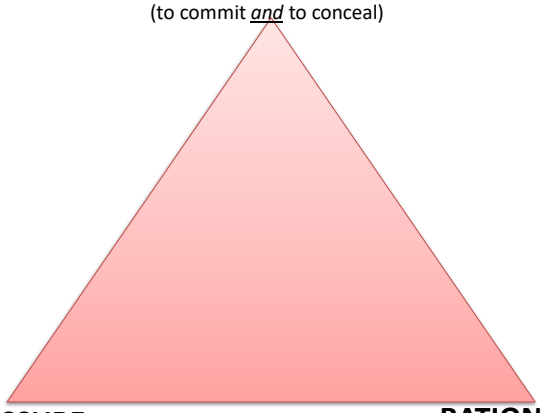
Idea to Consider



Fraud Triangle

Donald Cressey, Other People's Money, 1973
Joseph Wells, Occupational Fraud and Abuse, 2001

OPPORTUNITY
(to commit *and* to conceal)



DIRECT PRESSURE
("It's either greed or need")

RATIONALIZATION
(I'm worth it; I've been treated unfairly)

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Fraud Triangle

OPPORTUNITY
(to commit *and* to conceal)

Data fraud ONLY occurs when ALL THREE points are present

- Lori Richards, Director, Office of Compliance Inspections and Examinations Securities and Exchange Commission, September 2008

DIRECT PRESSURE
("It's either greed or need")

RATIONALIZATION
(I'm worth it; I've been treated unfairly)

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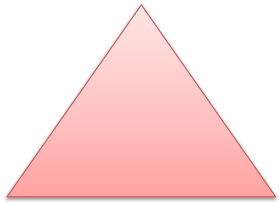
Data Fraud Happens - But

- It probably is the exception, rather then the norm
- Although EVERYONE at a firm has a financial incentive for success with a product batch, a lab test, incoming raw materials acceptance – EVERYONE
- ONLY a very few people have a **DIRECT** financial incentive

- Just because a company has an absence of a data integrity control …
  - ≠ poor data integrity
  - ≠ incentive for fraud to occur



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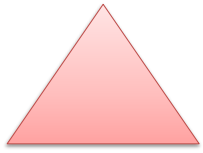
Line Worker Data Integrity Pressures

Joe is the factory floor shift supervisor. He's been at the drug firm for 14 years.

Tonight he has his first date since he broke up with his last girlfriend. He's leaving no later than 5pm no matter what.

The manufacturing system, eLimity, is slower than usual today and if they can't get the batch measurements entered into the system by 4:30pm, he'll have to stay late again.

What fraud corners (opportunity, direct pressure, rationalization) are present?



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Key Question

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Data Integrity Definition

Data have integrity "if they are **fit for their intended uses** in operations, decision making and planning" (J.M. Juran)

- http://en.wikipedia.org/wiki/Data_quality

Is the data "fit for use" in making product safety, efficacy and/or quality decisions…?

**Note: In the final 21 CFR 11 rule and preamble, "integrity" is referenced 50+ times*

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WHO Data Integrity Importance

"Implicit in the assessment and review process is **trust** between the regulator and the regulated **that the information submitted in dossiers and used in day-to-day decision-making is comprehensive, complete and reliable**. The data on which these decisions are based should therefore be complete as well as being attributable, legible, contemporaneous, original and accurate, commonly referred to as 'ALCOA.'"


Annex 5

Guidance on good data and record management practices

Background

- WHO, *Guidance on Good Data and Record Management Practices, June 2016*

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What Controls Exist Over?

- raw data
- graphs and visual analyses
- training files
- investigation files
- complaint and AE files
- calibration data
- lab notebooks
- product inventory and distribution
- digital patient diaries
- supplier qualification reports
- production batch records
- validation records
- incoming acceptance test results
- distribution records
- SOPs, policies, and forms

…and so on

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Records, information, raw data, etc. → Analysis, processing, storage, archival, etc. → Poor record integrity, sloppy Part 11 controls, weak RIM, etc. → Decisions on product and consumer safety from **dangerous data**

Poor Record Integrity
- FDA-483 observation
- Warning letter
- Untitled letter
- Consent decree
- Criminal prosecution
- (product liability litigation)
- (disgruntled shareholder litigation)

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Records, information, raw data, etc. → Analysis, processing, storage, archival, etc. → Poor r d integrity, y Part 11 contr etc. → Decisions duct and cons safety f gerous data

What controls do we have in place to prevent or to detect and mitigate?

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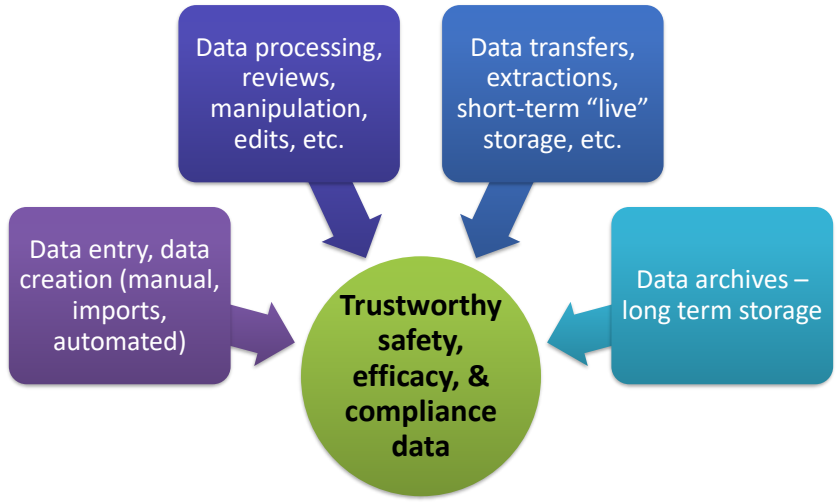
What Controls Exist Over…?



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Rapid Red Flag Question #1

Does the firm have a ***relatively current*** **Records Retention Schedule (RRS) and policy**?

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RRS Example for IT

Department	Record Types	Archived Retention	Citation
IT Systems Administration	COTS SW Code (DVDs, etc.)	End of SW Usage + 3 years	UPPBRA 31-08.1-02
	SW licenses & EULAs	End of SW Usage + 4 years	COV 8.01-243
	SDLC, configuration, and QC testing documentation	End of system life + 3 years	UPPBRA 31-08.1-02
	Leased HW disposal records (lists, receipts, etc.)	Date of disposal + 4 years	COV 8.01-243
	Owned HW disposal records	Date of disposal + 3 years	UPPBRA 31-08.1-02
IT Security	System Access Controls, User Account Lists, Security Configurations	Annual + 3 years	UPPBRA 31-08.1-02
	Personnel Medical Records System Access Controls, Security Config., Reports	Annual + 6 years	45 CFR 164.316 (HIPAA)
		Last Updated	July 2016

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Rapid Red Flag Question #1

Does the firm have a ***relatively current*** **Records Retention Schedule (RRS) and policy**?

If you don't know what you need to keep and for how long,
You cannot control it.

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Rapid Red Flag Question #2

Ask senior management, **Can you explain the relationship between good data integrity (e.g., data trustworthiness) and product safety, efficacy, and quality?**

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Senior Management Activities

- Act as sponsor of the overall data integrity program
- Review and approve budgets, assign resources
- Review and approve the overall site data integrity compliance plan (or the overall clinical trial data integrity plan)
- Help drive priorities based on a mix of risk and low-hanging fruit (create a "succession of successes")
- Keep program's focus on controlling risk to data and decisions ("How will this help our data be more trustworthy for….?")
    - decisions related to product safety and efficacy
    - decisions related to quality system and regulatory compliance

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Rapid Red Flag Question #2

Ask senior management, **Can you explain the relationship between good data integrity (e.g., data trustworthiness) and product safety, efficacy, and quality?**

If you cannot explain it,

You cannot lead it.

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Rapid Red Flag Question #3

How often **does the Quality Unit audit the data backups and long-term archives**?

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Example Warning Letters

This is all about storing data with integrity throughout the data lifespan

"Failure to prevent u to data and to provide adequate controls preventing data omissions. Our investigator requested the original electronic raw data. Your quality unit, after consulting with the Information Technology (IT) department, stated they were **unable to retrieve the original electronic raw data because back-up discs were unreadable**. Your quality unit then stated that **back-up disks have been unreadable since at least 2013**. However, **without complete, accurate, reliable, or retrievable raw data**...."

- Warning Letter to VUAB Pharma, May 2015
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm448433.htm

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"Documents and e-data spend **more than 80% of their lifespan** in an archived (*e.g.*, stored) state. "

- ARMA International

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Is This a Data Integrity Issue…?

For a product produced two years ago, a firm used a graphical product insert and label (it's got pictures on it plus text).

During an inspection, you request to see the original digital proof (with the firm's approvals to proceed, etc.) to ensure it matches with the approved labeling. After 4 days, this is **all that the firm could recover** from its original approved digital proof.

Is this acceptable since the firm does have paper copies of the graphical insert and label based on the digital proof?

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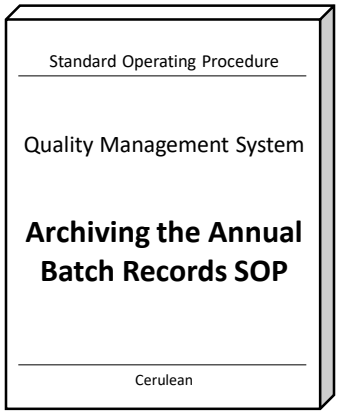
Example SOP Questions for Data Integrity during Long-Term Archives

- How often are archived data brought back from archive and sampled for consistency, integrity, completeness, etc.? Who is involved in this verification? Are they qualified?
- Is the data sampling scientific or otherwise a validated sampling methodology?
- Does the SOP give any indication on how missing/corrupt data in the archives are to be handled?



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True or False

___ As long as data is stored in PDF format, it will last forever

___ As long as data media – hard drives, tapes, CD/DVDs, etc. – are stored under environmentally controlled conditions, the data on them lasts forever

___ FDA should not care about long-term data archival – only the most recent set of records a firm has

___ Just relying on the once-in-a-while file restoration that IT usually does is more than enough to prove that long-term records are being maintained for regulatory compliance

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Example Data Archival Issues

sticky-shed syndrome
(moisture or oxide shedding)

disc-rot
(chemical degradation)

software-rot
(dormant v. active)

rodents
(physical damage)

bit-rot
(data degradation)

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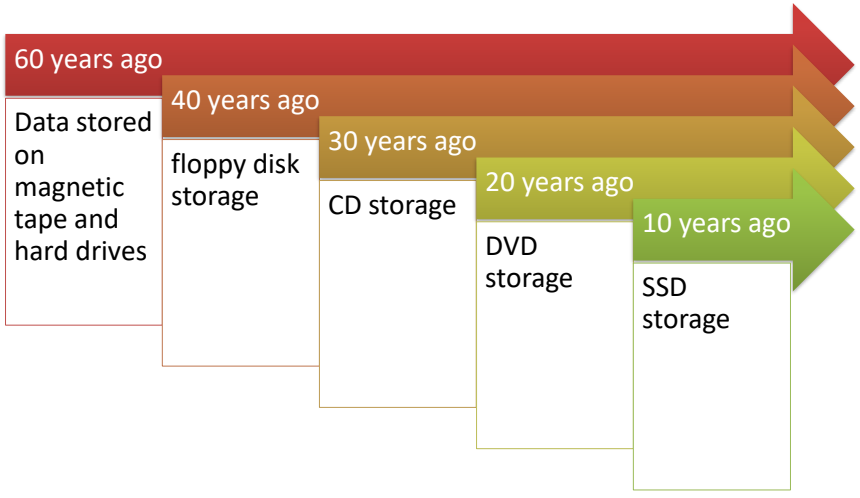
Bit Rot



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"So what?"

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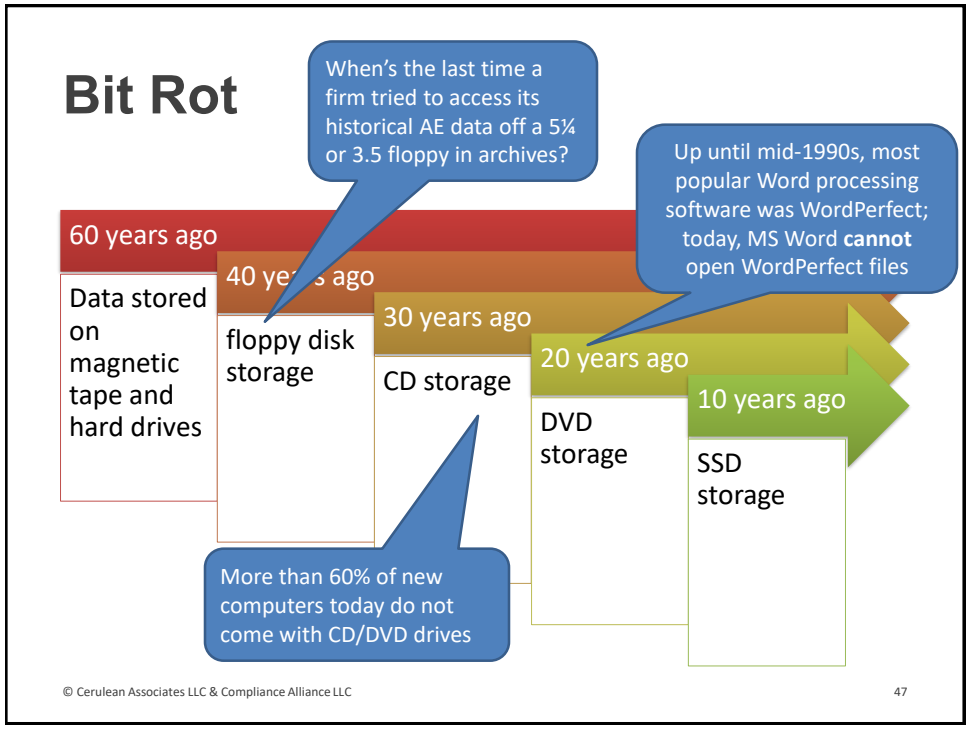

Typical Media Format Lifetimes

Media Type	Proven Archival Lifespan Range
Magnetic hard drive	3-5 years
SSD hard drive	Unknown (similar to USB at 5-10 years)
Analog tape	10-20 years
Digital tape	Up to 10 years
Floppy disk (3.5, 5¼, et al)	10-20 years
CDs/DVDs (recorded)	2-7 years
Blu-ray DVDs	Unknown (likely similar to CDs/DVDs)
Microform (microfiche/microfilm)	40-55 years (to date)

Sources:
Carnegie Mellon
Ars Technica
US National Archives and Records Administration
Recovery Zone

Silent Data Corruption

- Radioactive particles bombard the earth constantly
- Estimated to impact approx. 1.4% of data storage media per year
  - IBM estimates approx. 1 data corruption event per 256mb data stored – see www.scientificamerican.com/article/solar-storms-fast-facts/)
  - Amazon & Google have calculated similar numbers in the cloud (http://perspectives.mvdirona.com/2012/02/observations-on-errors-corrections-trust-of-dependent-systems/)
- Read more online (en.wikipedia.org/wiki/Data_corruption)

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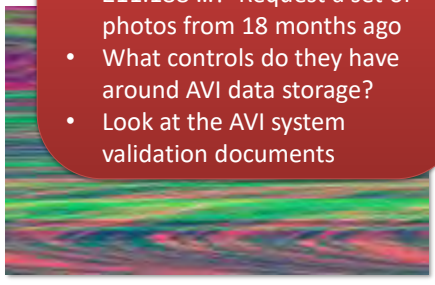
Video and Photo Retention

- **Prioritize long-term readability** over being able to edit photo
- Photos:
  - JPEG
  - TIFF
- Videos:
  - Evolving
  - MPEG-2 (.mp2) and MPEG-4 (.mp4) are best bets now

If a firm is using an AVI system during production…
ASK

- Are they retaining the photos or videos as per 21 CFR § 211.188 …? Request a set of photos from 18 months ago
- What controls do they have around AVI data storage?
- Look at the AVI system validation documents



Corrupted PhotoShop Photo from July 2014 GMP Tablet Release Camera

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Rapid Red Flag Question #3

How often **does the Quality Unit audit the data backups and long-term archives?**

If you don't ensure controls work throughout the data's lifespan,

You cannot have trustworthy data.

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Six Key Records to Request

1) Current records retention schedule policy
2) Good data integrity practices policy
3) Internal Quality Unit audit schedule
4) SOP on reviewing data and audit trails

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Audit Trail Reviews in 300 Seconds

"Manufacturers and analytical laboratories are **not expected to implement a forensic approach** to data checking on a routine basis, but instead design and operate a system which **provides an acceptable state of control based on the data integrity risk**, and which is fully documented with supporting rationale."

- MHRA, *GMP Data Integrity Definitions and Guidance for Industry*, March 2015

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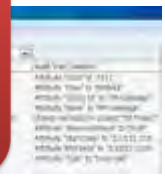
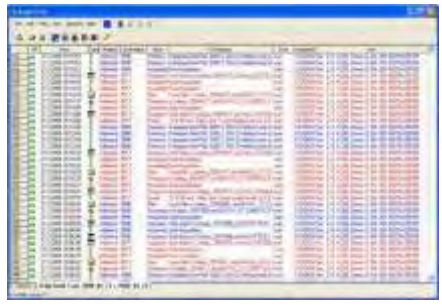
Audit Trail Reviews in 300 Seconds

- Date/time stamps
- User logins
- Tracking of regulated activities
- Tracking of data file activities
- Reviewing for potential issues
- Forensic investigations
- Troubleshooting
- System changes

By and large, we are talking about simple APPLICATION AUDIT trails – not all the detailed Windows or System Root audit trails





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Example Extract – Can You Spot the Problems…?

Mary Jo says she tested 8 samples from lot # 250 – all passed. Here's the audit trail from the system:

Product Sample Name		Filename
Lot# 250 REP1	17:13:19	0[illegible]
Lot# 250 REP2	17:17:10	090811-004.rst
Lot# 250 REP5	18:28:19	090811-007.rst
Lot# 250 REP5	18:34:07	090911-007-20110809.rst
Lot# 250 REP6	[illegible]	[illegible]1-008.rst
Lot# 260 REP7	[illegible]	090811-009.rst

Where are REP3 and REP4 and their data files…?

There's a 1 hour 21 minute gap…why?

Was this product sample tested twice?

Why does the 6th test reference a different lot #?

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Six Key Records to Request

1) Current records retention schedule policy
2) Good data integrity practices policy
3) Internal Quality Unit audit schedule
4) SOP on reviewing data and audit trails
5) Site computerized system inventory list

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¡Caution! Inventory Lists

- This is NOT want a comprehensive listing of all systems and software
- This is ONLY a list of **computerized systems used principally for regulatory purposes** – *and not just capital systems* (e.g., must include spreadsheets with macros, spreadsheets used for manipulating raw data, local Access databases, software used for monitoring critical T° and pH, etc.)

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Regulator's Computerized System Inventory Format*

And here is a nice list of change controls you can request to see

Type	Area/Site	Product Name, Purpose & Supplier	Version or Model	Last Validation Date	Most Recent Changes (within past year)
Networked (onsite)	Labs (all)	Chromeleon Chromotography Data System (Thermo Scientific)	v 6.9	Dec. 2014	Change controls #73, 76, 81
Hosted SaaS	Corporate (all sites)	TrackWise EQMS (Sparta)	v 8.1	Nov. 2015	Change controls #81, 111
Stand-alone	QC Lab	Excel Sample Tracking Worksheet (Microsoft with custom macros)	v Office 2013	April 2016	n/a

And look – here are the PQ's you should consider looking at

*Source: MHRA Inspection Notification Letter

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Six Key Records to Request

1) Current records retention schedule policy
2) Good data integrity practices policy
3) Internal Quality Unit audit schedule
4) SOP on reviewing data and audit trails
5) Site computerized system inventory list
6) Site data integrity compliance plan

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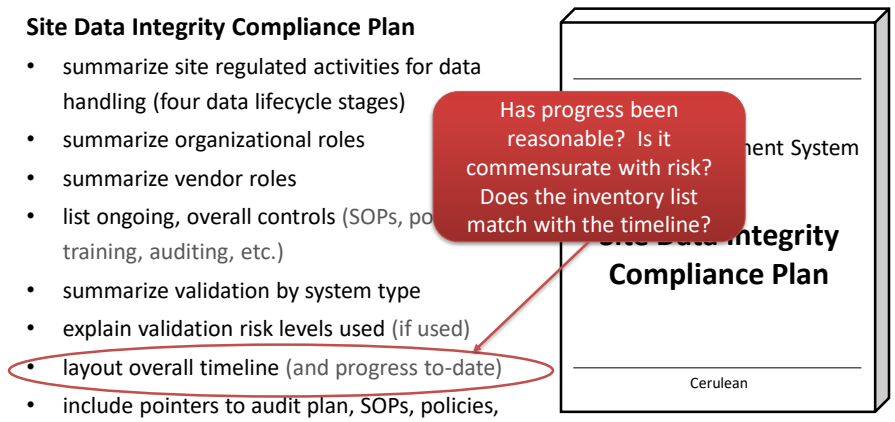
Plan Elements

Site Data Integrity Compliance Plan

- summarize site regulated activities for data handling (four data lifecycle stages)
- summarize organizational roles
- summarize vendor roles
- list ongoing, overall controls (SOPs, po training, auditing, etc.)
- summarize validation by system type
- explain validation risk levels used (if used)
- layout overall timeline (and progress to-date)
- include pointers to audit plan, SOPs, policies, completed validations, etc.
- site senior management should sign-off on



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Conclusion

When you think about data, make sure it conforms to ALCOA.

- **A**ccurate – data are correct with no unknown/undocumented errors
- **L**egible – data are readable by humans throughout the retention period
- **C**ontemporaneous – data are recorded at the time they are generated or observed
- **O**riginal – data are the original observations (or are certified or "true copies")
- **A**ttributable – data are identified with a specific subject and a specific individual who recorded it, analyzed it, edited it, etc.
- **https://www.youtube.com/watch?v=wKsdMenonLw**

About Your Presenter
John Avellanet

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John Avellanet gives practical, compliance solutions for clients around the world. Winner of the 2009 & 2011 Best of Business Services award by the Small Business Commerce Association, Mr. Avellanet has earned international acclaim for his business-savvy, pragmatic compliance advice.

He most recently served as the industry expert reviewer for the international standard, BSI 10008 *Evidential Weight and Legal Admissibility of Electronic Information* (2015). He is a lead expert for the ISPE GAMP Data Integrity Working Group.

In 2014, he co-authored the book, Pharmaceutical Regulatory Inspections, with several current and former regulatory agency officers, and his industry classic, Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine (2010), was originally featured at BIO 2011 and garnered multiple five-star reviews from industry publications, blogs, Amazon.com readers, and former FDA officials.

From 2011-2015, John served as the Independent Review Organization on behalf of the US Department of Justice over the multi-million Dr. Comfort corporate integrity agreement.

Prior to founding Cerulean, John spent more than 15 years designing, implementing, and being accountable for quality systems and data compliance programs for FDA, DEA, BIS, ICH, IMDRF, and ISO.

In 2006, Mr. Avellanet founded his independent consulting and training firm, **Cerulean Associates LLC**.

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About Your Presenter
Nancy Singer

nancy@compliance-alliance.com

Nancy Singer founded Compliance-Alliance LLC to specialize in the professional development for those employed in the medical device and drug industries. Previously she served as AdvaMed's Special Counsel for FDA compliance and enforcement matters.

Nancy began her career as an attorney with the United States Department of Justice where she did litigation for the Food and Drug Administration. Subsequently she was a partner at the law firm of Kleinfeld, Kaplan and Becker.

Nancy received her B.S. from Cornell University , and J.D. and LL.M. degrees from New York University Law School.

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