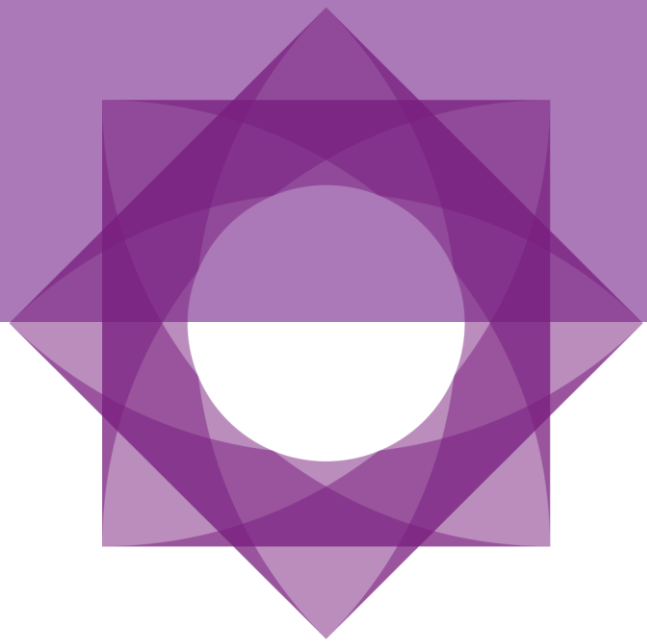
Data Integrity – In 2017 with some specific ECM cases

18th May 2017

Keith Williams



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Data Integrity

Agenda

- Introduction
- Data Integrity- some definitions
- Audit trails
- System vs Record lifecycle
- Some Common Data Integrity Issues
- Regulatory Perspective in US and Europe
- Recent examples
- Use case and My thoughts with respect to Enterprise Content Management systems
- Questions

Introduction - Keith Williams and Formpipe

- An engineer, entrepreneur, director, with UK, European and US experience.
- 30 years of Life Sciences experience, known for a pragmatic approach to getting computerised systems compliant and keeping them compliant.
- Worked in manufacturing, laboratory and clinical environments
- Built computerised systems to manage Compliance, Quality and Risk across an organisation on a single platform.
- Formpipe provides solutions for electronic document management, Quality management, case management, long term record retention and ERP integration.
- Member of GAMP® Europe Steering committee.

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Data Integrity

What is data Integrity?

- The assurance that data records are accurate, complete, intact and maintained within their original context, including their relationship to other records

- This applies to data recorded in electronic and paper formats or a hybrid of both

- “The extent to which all data are complete, consistent and accurate throughout the data life cycle” *MHRA Data Integrity Definitions and Guidance, Revision 1.1 March 2015*

What are we actually talking about?

- Protect original data from
  - Accidental / malicious modification
  - Falsification
  - Deletion
- Data needs to be Attributable, Legible, Contemporaneous, Original, and Accurate (**ALCOA**)
  - Following Good Documentation Practices

FDA vs EMA- Data Integrity

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FDA: ALCOA

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

EMA: ALCOA +

- Complete
- Consistent
- Enduring
- Available

Clinical Real example- Paper vs Electronic vs hybrid

Modality	A	L	C	O	A
Paper	SC Signature	Printed with subject ID	Timed and dated entry	Source document worksheet	PI co-sign next to entry
eCRF	SC credentials	Typed and linked to subject	Time/date in audit trail	No paper	PI sign page
Hybrid	Paper scanned to CD				

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Audit trails

What is an audit trail?

- 21 CFR Part 11 - § 11.10 Controls for closed systems.
- (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

- EU GMP Annex 11 - 9. *Audit Trails*
- Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

What should we be doing with the Audit Trail?

- Review it!
- Numerous factors to consider, criticality of the data, regulatory scrutiny, available resource, human behaviour, etc.
- As part of the close out of a study, an analysis or batch?
- Monthly
- Quarterly
- As part of the periodic review programme

- Audit trail review should be part of the routine data review / approval process, usually performed by the operational area which has generated the data (e.g. laboratory) (MHRA)

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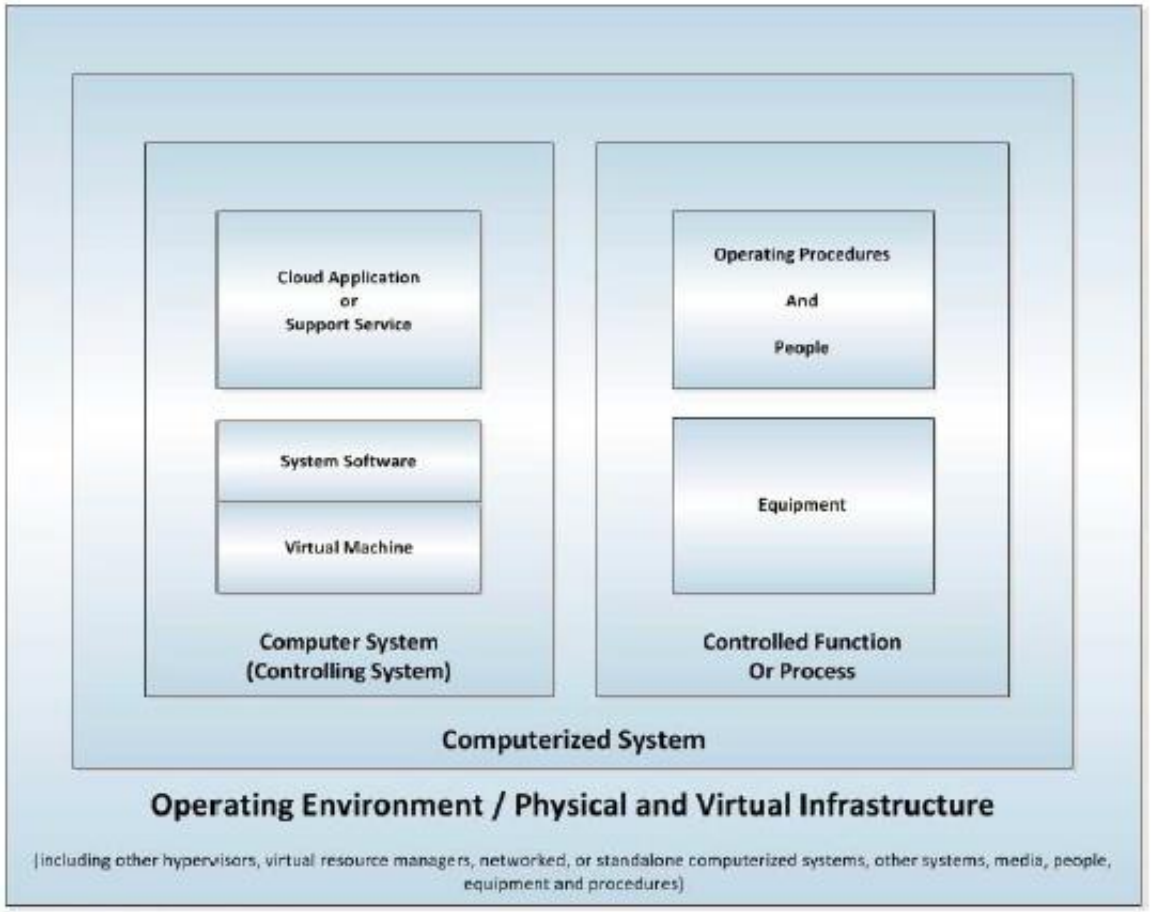
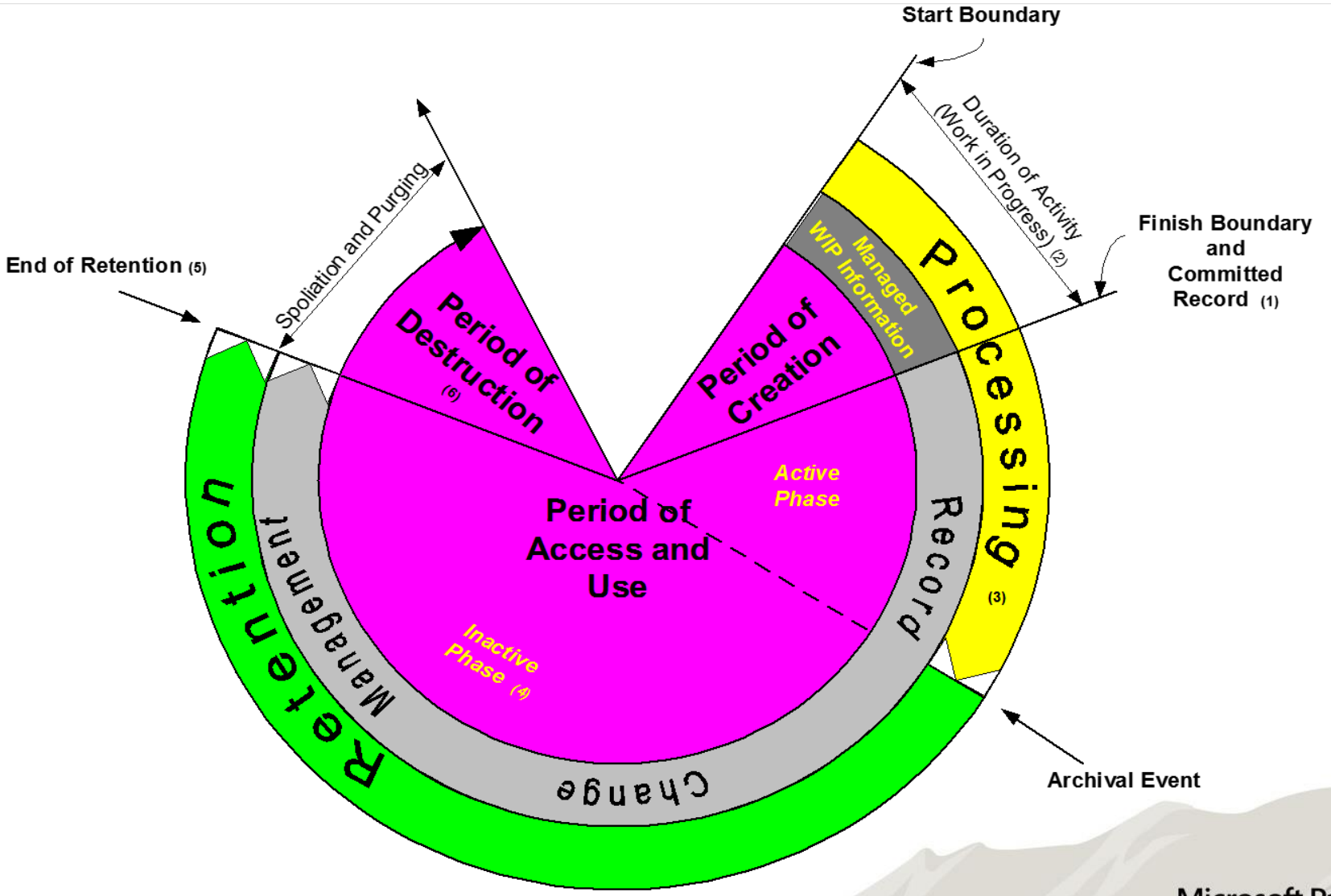
System vs Record Lifecycle

Computerised System



PIC/S diagram of a Computerized System

Electronic Record
System Lifecycle vs Record Lifecycle



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Some Common Issues

What are the outcomes of Data Integrity (Data corruption) problems?

- May compromise the safety / efficacy / quality of products
- Increase risk of non-compliance with GxP's
- Regulatory Authorities to initiate product recalls or impose import bans

Common Data Integrity Issues - 1

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Common passwords	Analysts share passwords, unable to identify who created or changed a record
User privileges	System configuration does not adequately define or segregate user levels Users have access to unauthorised functions
Computer System Operational Controls	Inadequate controls over data Unauthorised access to modify or delete files No automatic saving of files, records not accurate or complete
Processing methods	Integration parameters not controlled, chromatograms may be re-integrated without correct change process
Audit trails	Functionality turned off, no complete record of the data life cycle – who modified a file and why

Common Data Integrity Issues - 2

Conflict of interest	Business process owners granted enhanced security access e.g. system administrator
"Unofficial" documentation	Recording data first on a scrap of paper then transferring to the official document (e.g. the laboratory notebook)
Failure to review "original data"	Data and metadata not reviewed together to ensure context is maintained Errors or omissions may be undetected
Inadequate data retention arrangements	Failure to avoid inadvertent or deliberate alteration or loss throughout the retention period

Regulatory Position

What they say about data

FDA	MHRA	WHO
Completeness, **consistency**, and **accuracy** of data.	The extent to which all data are **complete**, **consistent** and **accurate** throughout the data lifecycle.	Degree to which a collection of data is **complete**, **consistent** and **accurate** throughout the data lifecycle.

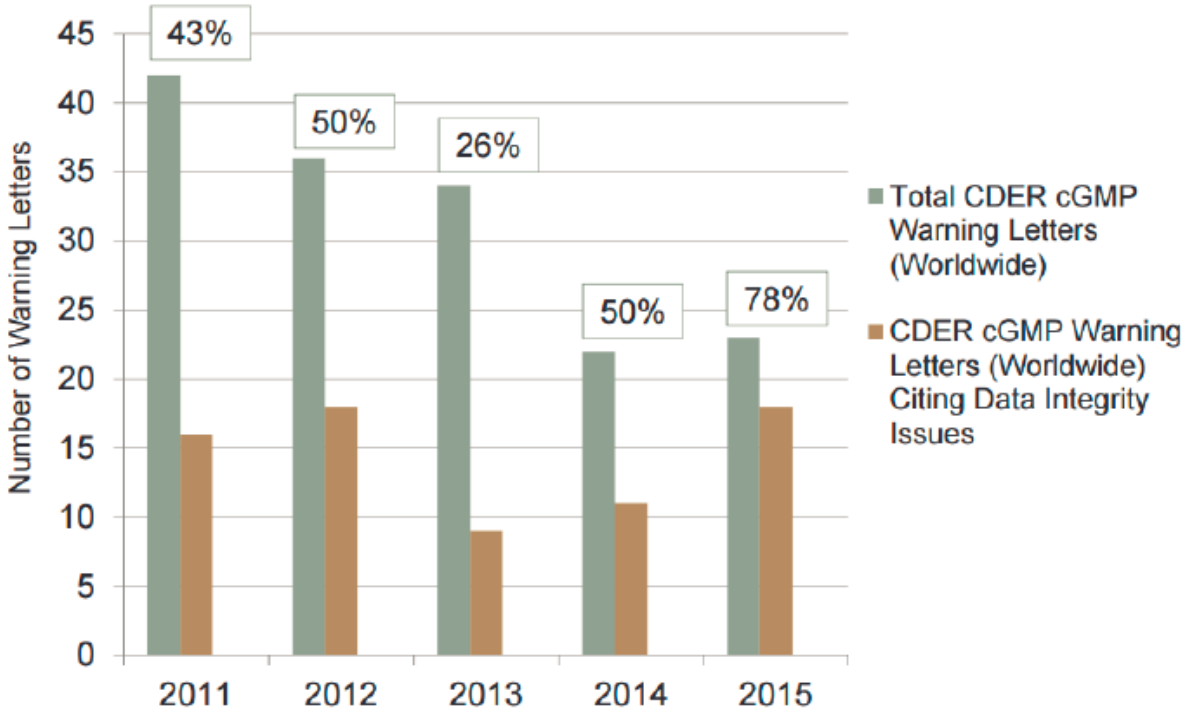
Why is Data Integrity Important?

- Regulatory agencies, as well as industry, rely on accurate information to ensure drug quality
- Data integrity problems break trust between industry and regulatory agencies
- Regulatory agencies rely largely on trusting the firm to do the right thing when they are not there

Reference: *Karen Takahashi, Senior Policy Advisor FDA*
ISPE/ FDA/ PQRI Quality Manufacturing Conference, 1-3 June 2015, Washington, D.C.

FDA Warning letters- % Data integrity

Data Integrity Issues



"International Pharmaceutical Supply Chain Imperiled Like Never Before"; Webinar Presented by Dechert LLP and Hyman, Phelps & McNamara PC; June 2016

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Recent Examples

Recent Data Integrity Findings - 1

Seikagaku Corporation	December 2013	Competent Authority of Sweden	2003/94/EC (EU GMPs)
The critical deficiency concerns systematic rewriting/manipulation of documents, including QC raw data. The company has not been able to provide acceptable investigations and explanations to the differences seen in official and non-official versions of the same documents.			

Recent Data Integrity Findings - 2

Micro Labs Ltd	May 2014	WHO Notice of Concern	WHO ref. 15.9, 17.3d, 15.1

HPLCs did not have audit trails enabled, some audit trails missing when peaks were manually integrated, no SOP to describe when manual integration is acceptable. Some instruments had date and time functions unlocked and were not linked to a server, so timestamps could be manipulated. One HPLC had a shared password so actions were not attributable to an individual. In some cases, trial injections were made but were not part of the test record.

Recent Data Integrity Findings - 3

Cadila Healthcare Ltd	December 2015	FDA Warning Letter	211.68(b)

Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.

....laboratory manager had the ability to delete data from the Karl Fischer Tiamo software....found that one file had been deleted. However, because the audit trail function was not activated, and because eight different analysts share a single username and password, you were unable to demonstrate who performed each operation on this instrument system.

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Use Case example

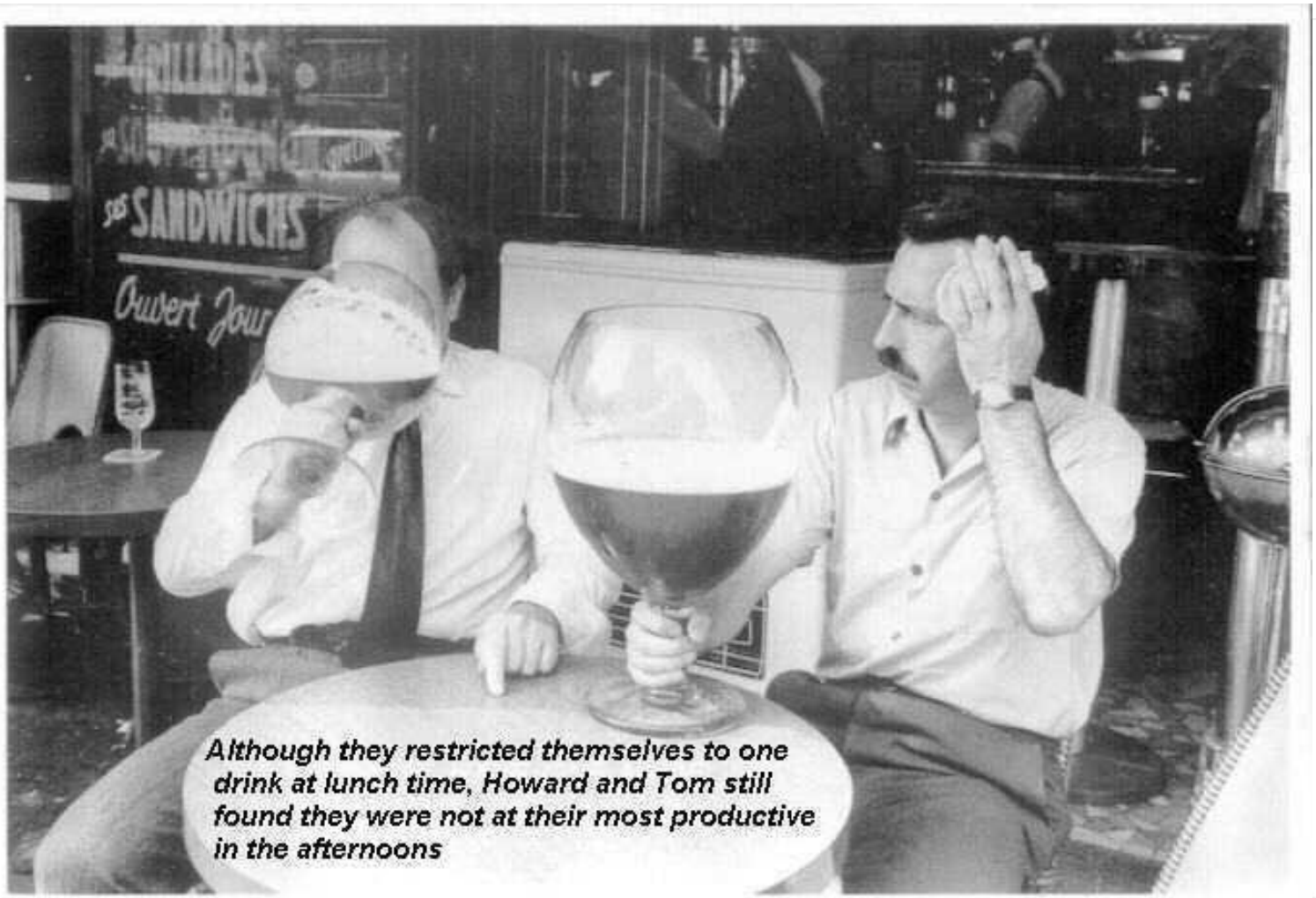
Use Case – Audit Trails in ECM

- Lots of focus on audit trails- what data is of value?
- We have products that can audit everything, we had customers who wanted to audit everything (every site visited, every page rendered, system calculations)
- Just because it is possible, should you capture everything?
- What elements are required to maintain the integrity of the record?
- What are material changes to an electronic record?
- Does visiting a document site make a material difference to its content?
- Record retention is the longer term problem (see Preservation Formats at the end)

Data integrity- My reflections

- *As with the whole presentation these are my thoughts and are not the position of Formpipe (my employer) and Epista who asked me to speak here.*

Although we are talking digital, fundamentally it is still about people…….



QUESTIONS

Thank You

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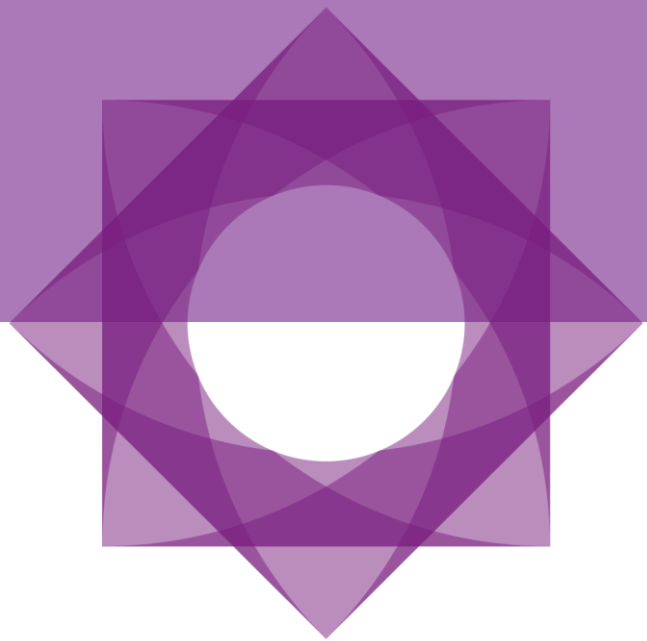

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Example Content Types and Preservation Formats

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Content Type	Description	Example Application	Native Format	Preservation Format
Formatted document	Sometimes called 'office documents'; made up of a combination of alphanumeric and special characters, sometimes with embedded graphics, video, audio or other types.	Any 'office' suite, email programs, Acrobat	DOC, DOCX, GDOCS, ODF, OOXML, PDF, PPT, PPTX, W51, XLS, XLSX	PDF/A
Alphanumeric (unstructured) data	Files made up of alphanumeric (and other printable) characters that do not depend upon formatting.	XML authoring tools, other specialised text editors	DTD, TXT, XML, XLST	TXT XML
Instrument data	Results from laboratory instruments, typically in proprietary format.	Laboratory instruments	CSV, MI, MX, SMR, SMS, SPA, SPG, WSV	CSV XML
Database	Data structured so as to allow analysis, reporting, etc.	Access, other database packages, statistical analysis software	MDB, DB, DBF, GRDB	CSV XML
Image	Graphics formed from bitmaps (rasters), or vectors, in monochrome, greyscale or color.	Scanners, vector graphics programs, image editors	AI, BMP, CDR , DNG, JPEG, PNG, RAW, TIFF	Several alternatives
Audio	Speech, music or other sounds.	Sound recording and editing software	AAC, DTS, FLAC, MP3, WAV, WMA	Several alternatives
Video	Moving images, with or without sound.	Video recording and editing software	AVC, AVI, FLV, MOV, MP4, WMV	Several alternatives
Website	Internet and intranet sites, including blogs.	Web authoring packages	ASP, CSS, HTM, HTML, MHT	WARC

Data integrity in Clinical- regulations

- September 2015 MHRA issued a position statement and guidance on electronic health records-why?
  - They were seeing systems launched without suitable controls
  - Patients couldn't participate in clinical trials because of deficient EMR/EHRs
- FDA followed suit in May 2016 with draft guidance
  - Use of Electronic Health Record Data in Clinical Investigations

Data integrity in Clinical- what are they looking for?

- Maintenance of data integrity by ongoing data review, change control processes and audit trails
- Complete audit trail for information added to EHRs
- Access to the system should be available for inspectors and sponsor representatives (monitors and auditors) limited to trial patients.
- Appropriate archiving to ensure reliability, reproducibility and retrieval of data
- Expectation of suitable disaster recovery/ business continuity procedures
- Expectation of system validation and change control of the system

Other Regulatory Position papers and guidance

MHRA GxP Data Integrity Definitions and Guidance for Industry
Draft version for consultation July 2016

FDA Data Integrity and Compliance with GMP – ***Guidance for Industry, April 2016***

WHO Guidance on Good Data and Record Management Practices, ***Sept 2015***

PIC/S Guidance Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, ***Draft Aug 2016***