常用儀器之電腦化系統確效及數據完整性

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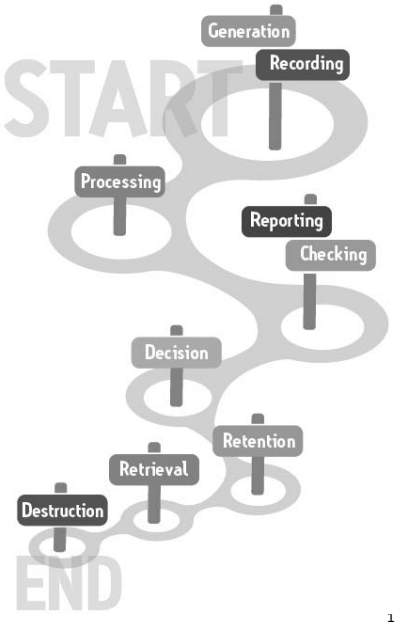


Agenda - I

- Data Integrity
- Regulatory Finding
- Explaining Specific Finding
  - Reanalysis
  - Reprocessing

Data Integrity

Data Integrity: Regulatory Findings

Explaining Specific Findings

- Reanalyzing into Specification
- Reprocessing into Specification

What is Data Integrity?

integrity

/ɪnˈtɛgrɪti/

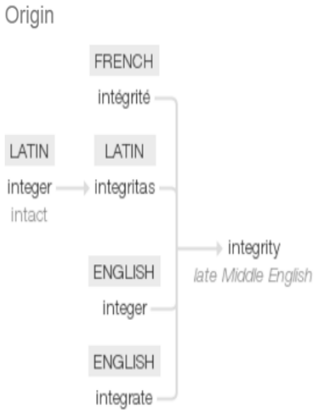
1. the quality of being honest and having strong moral principles.

   synonyms: honesty, uprightness, probity, rectitude, honour, honourableness, upstandingness, good character, principle(s), ethics, morals, righteousness, morality, nobility, high-mindedness, right-mindedness, noble-mindedness, virtue, decency, fairness, scrupulousness, sincerity, truthfulness, trustworthiness

   antonyms: dishonesty

2. the state of being whole and undivided.

   synonyms: unity, unification, wholeness, coherence, cohesion, undividedness, togetherness, solidarity, coalition



What is Data Integrity?

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Why the New Focus on Data Integrity?

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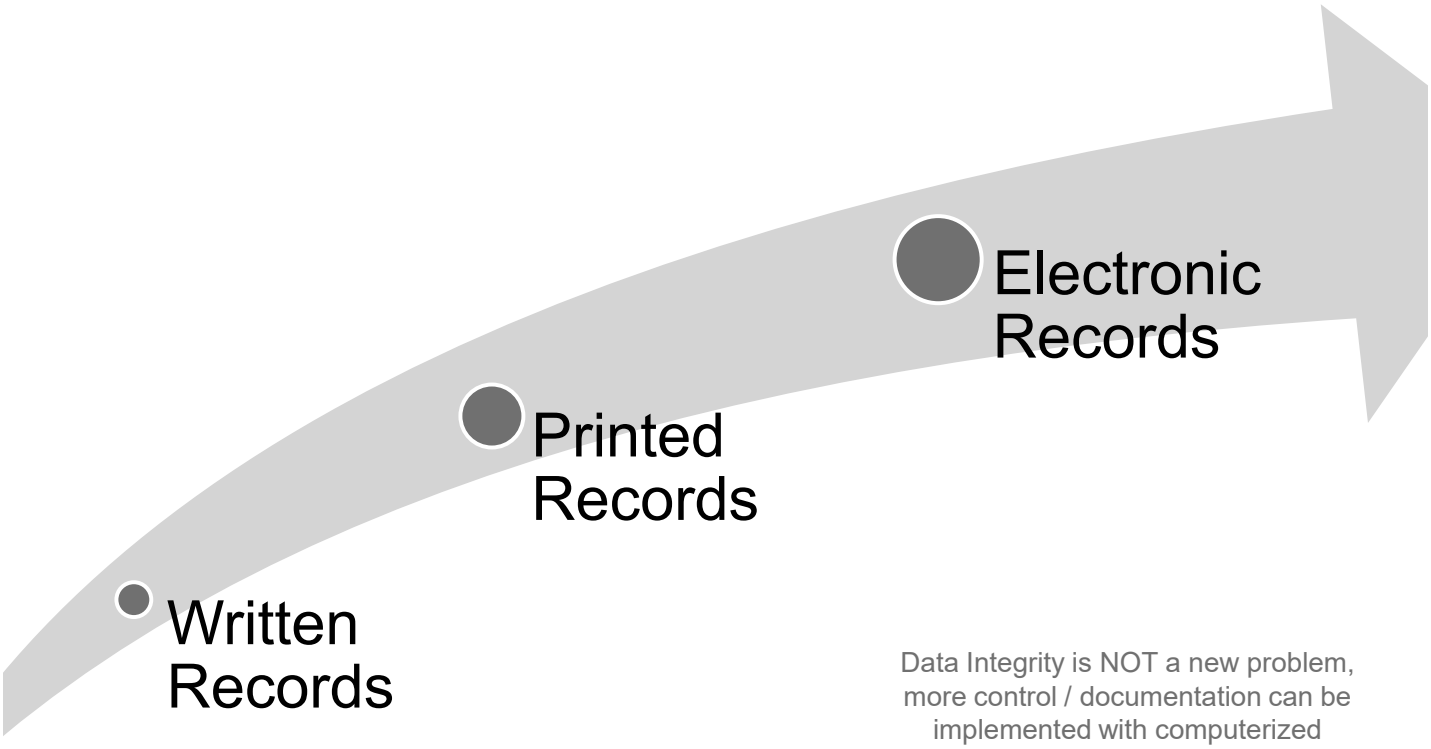
Electronic Systems Improve Traceability

Provide the **controls to prevent** but also **capability to detect** undesirable users actions

- Tools for QA and regulators
  - Access levels
  - System policies
  - Audit Trails

Agencies have lost the trust that analysts behave with honesty and integrity

Benefits of Computerised Systems for Data Integrity



Data Integrity is NOT a new problem, more control / documentation can be implemented with computerized systems

Why the new focus on Data Integrity?

Data integrity is not a new problem, more control / documentation can be implemented with computerized systems

Paper Documents	Computerized Systems	Improvements
Notebooks are issued to users	User accounts issued to users	Computerized systems can have access controls
Bound notebooks with pre-printed pages	Authentication, maintain raw data	Authentication provides increased assurance actions are performed by that user, raw data cannot be overwritten
Stamps with automatic data / time	System Generated Audit Trails	System control: for ALCOA (no back dating)
Initial, date, and user correction comments	System Generated Audit Trails	System control: for ALCOA (user / date associated to action cannot be altered)
Reviewed to ensure complete and accurate	Metadata is available for review	Review includes metadata
Handwritten signatures	Electronic Signatures	System control: for ALCOA (no back dating)
Archival of Data in		

Able Laboratories 483
May 2005

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Product/Batch Number	Lack of Complete Data
Products and batches listed in FDA-483, point #2	OOS results not documented in laboratory records. Unreported OOS results found in electronic data files.
Propoxyphene Napsylate and APAP Tablets, 100/650mg Batch 303110A	Changed chromatogram headers by cutting and pasting, so during review all sample injections would appear to be in sequence, for Dissolution Testing of Tablets D1 and D5
Propoxyphene Napsylate and APAP Tablets, 100/650mg Batch 104026B Validation Batch	Original Sample Weights not recorded in notebook. Sample weights were changed by the analyst until a passing result was obtained for Assay (A2)
Acetaminophen & Codeine Phosphate Tablets, 300/30mg Batch 407148	Processing methods changed by analyst until the processing method resulted in a passing result. Original processing method not recorded in laboratory notebook.

http://www.fda.gov/aboutfda/centersoffices/officeofglobalregulatoryoperationsandpolicy/ora/oraelectronicreadingroom/ucm061813.htm

Data Integrity:
Key for Quality Assurance

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Underlying Everything: Regulatory bodies need to trust the data they are seeing

- **Data Integrity Guidances:** focused on chromatography
- **Review of audit trails**
- **Focused Inspections:** All are focusing on Data Integrity
  - Several new guidances (at least five)
  - Static and Dynamic Data (static printed chromatograms)
    - Expect to look at the electronic data, not just printouts
  - Continual training of regulators in electronic laborat
- **Ensuring the bad as well as the good data**
  - Specifically for reanalysis and reprocessing
- **Find the root cause of issues and OOS**
  - Right scaled Lab error and Full OOS investigations

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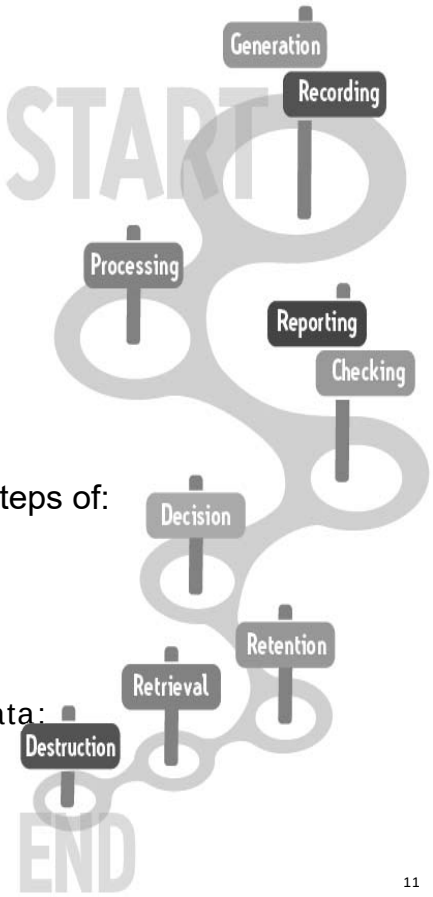
What is Data Life Cycle?

MHRA
Regulating Medicines and Medical Devices

- …from initial generation and recording through processing (including analysis, transformation or migration), use, data retention, archive / retrieval and destruction.

World Health Organization

- ...assessing risk and developing quality risk mitigation strategies for the data life cycle,
- including controls to prevent and detect risks throughout the steps of:
  - data generation and capture;
  - data transmission;
  - data processing;
  - data review;
  - data reporting, including handling of invalid and atypical data;
  - data retention and retrieval;
  - data disposal.



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Securing and reviewing complete data:

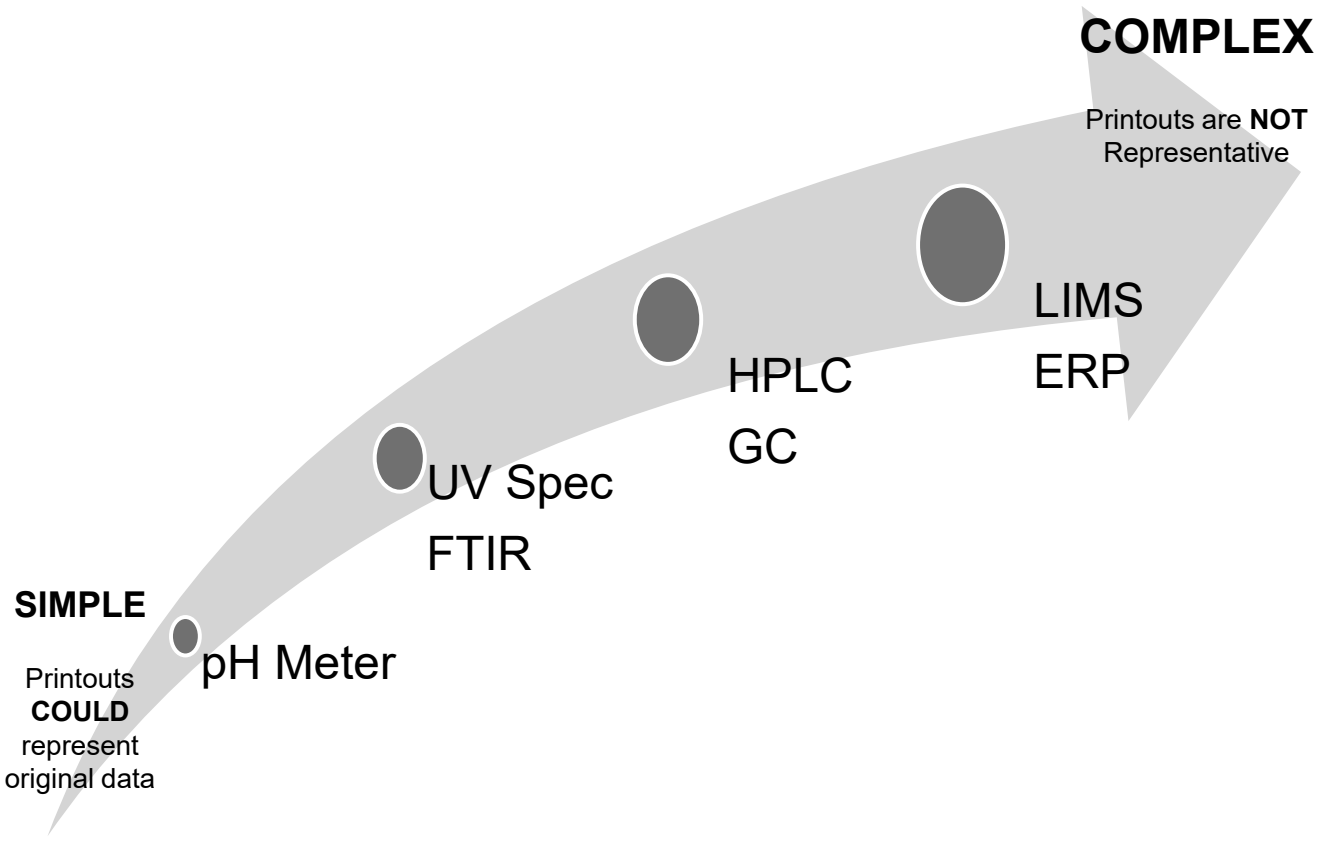
The regulators view of static and dynamic data

FDA Guidance – Records and Reports from 2010

"the **printed chromatograms** used in drug manufacturing and testing **do not satisfy** the predicate rule requirements in 21 CFR Part 211.

The electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator"

Paper Does Not Always Provide the Complete Story



Laboratory source e-records

From presentation of Robert D. Tollesen National Expert-Computers at FDA's ORA

ISPE GAMP Nov 2011 Brussels

e-data files from complex analytical systems (i.e.; Chromatography systems)

- Must be retained as per 21CFR211.194(a)
- Must be reviewed for completeness and accuracy and compliance with established standards as per 21CFR211.194(a)(8)
- Must be available for inspection as per 21CFR211.180(c)

- For simple instruments Paper or PDF may be complete

MHRA Draft GxP Guidance:
Reviewing Electronic Records Summary

- Data may be…
  - **Static** (e.g. a 'fixed' record such as paper or pdf) or
  - **Dynamic** (e.g. an electronic record which the user / reviewer can interact with).

- **Data must be retained in a dynamic form** where this is critical to its integrity or later verification.

- (Once printed) **chromatography records** lose the capability of being reprocessed and do not enable more **detailed viewing of baselines or any hidden fields.**

- Some data generated by electronic means to be retained in an acceptable paper or PDF format
  - Where it can be justified that a static record maintains the integrity of the original data.
  - Verified copies of all raw data, meta data, audit trail, result files, software/system configuration settings for each record, all data processing runs including methods and audit trails for a reconstruction …. and verification

  This approach is likely to be onerous to enable a GxP compliant record

GxP Data Integrity Definitions and Guidance for Industry
DRAFT July 2016

FDA Draft Data Integrity Guidance:
Reviewing Electronic Records Summary

- **Static** is used to indicate a fixed-data document (such as a paper record or an electronic image), and
- **Dynamic** means that the record format allows interaction between the user and the record content.
  - But defines as allowing the reviewer to change/edit things…???

- (Printouts allowed if) **includes associated metadata** and the **static or dynamic nature of the original records**

- Electronic records from certain types of laboratory instruments are **dynamic records**, and **a printout or a static record does not preserve the dynamic format**

Data Integrity and Compliance with CGMP Guidance for Industry
DRAFT April 2016

WHO Guidance:
Reviewing Electronic Records Summary

- **A PDF or printout is fixed or static** and the ability to expand baselines, view the full spectrum, reprocess and interact dynamically with the data set would be lost in the pdf or printout

- Data integrity **risks may occur when persons choose to rely solely upon paper printouts or PDF reports**
  - If the reviewer only reviews **the subset of data provided as a printout** or PDF, these risks may go undetected

- Paper printouts of original electronic records from computerized systems may be **useful as summary reports …verify that the printed summary is representative of all (electronic)results.**

- A risk-based approach to reviewing data requires **process understanding and knowledge** of the key quality risks.. requires **understanding of the computerized system, the data and metadata and data flows.**

Guidance on Good Data and Record Management Practices
Released June 2016 As WHO_TRS_996 Annex 5

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Data Integrity

Data Integrity: Regulatory Findings

Explaining Specific Findings

- Reanalyzing into Specification
- Reprocessing into Specification

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FDA presentation in June 2015

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Why is Data Integrity Important?

- We rely on accurate information to ensure drug quality
- Data integrity problems erode confidence
- We rely largely on confidence that the firm will do the right thing when we are not there

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

2nd Most Common Citation

- Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in the master production and control records, or other records (21 CFR 211.68(b)).
  - Cited in 15 warning letters

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

2nd Most Common Citation

- Cited in numerous warning letters:
  - Audit trails were disabled
  - A shared username and password was used by many analysts
  - Users were able to manipulate, delete, or overwrite electronic raw data
- Firm's laboratory practice is to print chromatograms and delete electronic raw data files

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- 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)).
  - Cited in 21 warning letters

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FDA presentation in June 2015

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Cited in numerous warning letters as failure to retain complete data:
  - "trial" sample injection data was not kept as part of the data for a batch
  - Sample weights, sample preparation and sample dilutions were not retained
  - Deleted data detected in audit trails
  - Overwriting data
  - Ripped up data found in the garbage

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FDA presentation in June 2015

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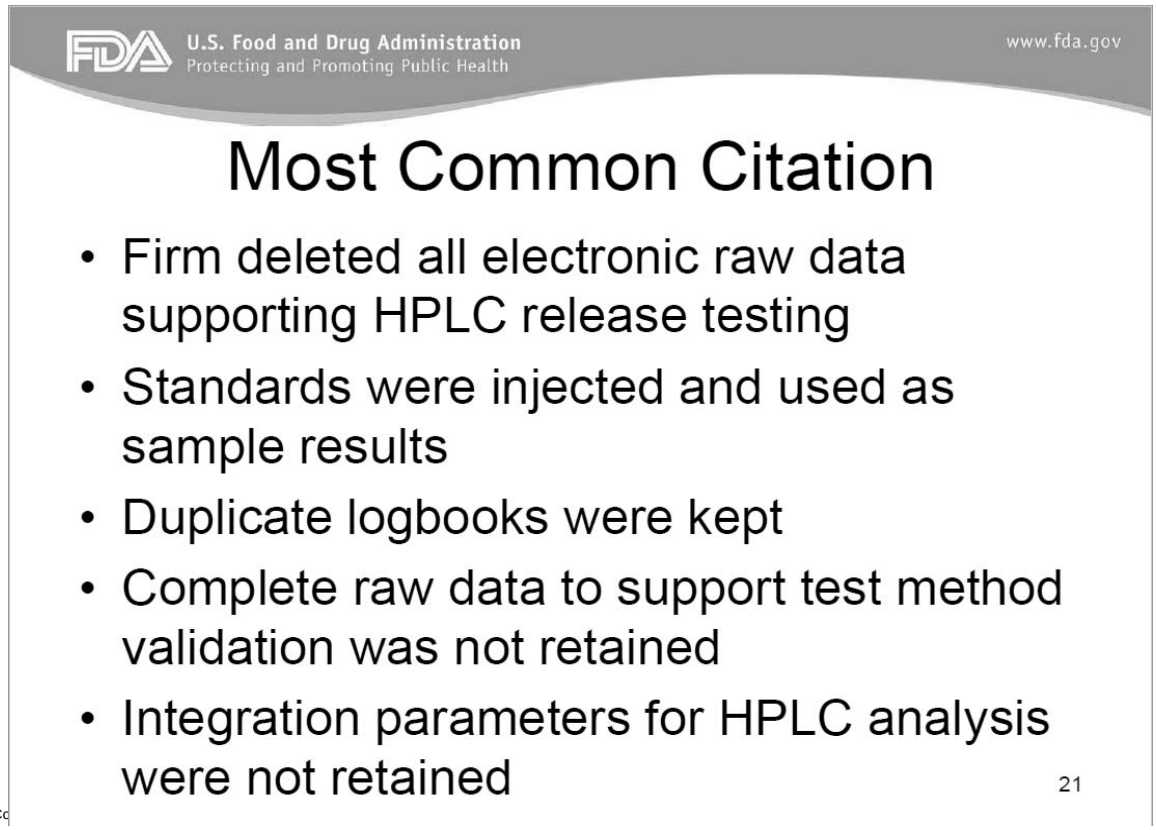

Data Integrity OK? Check your Process Flow

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- To balance the focus on electronic data, a useful approach is to map the workflow within the laboratory.
  - Identify and list all of the steps performed for each analytical technique (from sample receipt to approval of results) and each laboratory operation
- The mapping should identify:
  - What actions are performed?
  - How those actions are performed?
  - How they are recorded?
  - Any decisions made.
  - The extent to which the process is manual or automated
  - The possible risks associated with the step (e.g., how could fraud be prevented or detected)
- One of the purposes of data-integrity auditing is to actively look for evidence of fraud or the opportunity for fraud

21 CFR Part 211.194: Laboratory Records

All laboratory records required to be kept

Analytical
cations or Excel

Lab Book or forms

Lab Book or forms

Poor Technical Controls

Sharing Accounts

All laboratory analysts share the same password

Shared the same username and password

common PC login used by all ..analysts

..the analyst misused the administrator password to delete and overwrite the actual data logged in the audit trail

Unsecured Data

There is no system in place to ensure that all electronic raw data from the laboratory is backed up and/or retained.

your firm provided only the printed copies of the raw data

Missing /deleted / non existent data

Failure to have complete data as per 211.194

data was not consistently archived

Why Do Those Things Matter?

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Delete Privileges

did not have sufficient controls to prevent the deletion or alteration of raw data files

our inspection found 5,301 deleted chromatograms

Users can delete data

computer folders and files could be easily altered or deleted

Data is deleted to make space for the most recent test results

HPLC raw data files can be deleted from the hard drive

(no) access controls to prevent deletion or alteration of raw data.

HPLCs showed data was deleted

deleted electronic files with no explanation

data could be deleted using a common OS log on

your firm tested a batch sample six times and subsequently deleted this data

Data Deleted to Hide What?

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Data Manipulation

(no) proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data.

Ignoring failing injections and recalculating without

performing trial standard and sample analysis prior to official analysis is a standard practice

re integrations occur without a valid procedure

"unofficial" testing outside Enterprise CDS and not reported, or retested till passing

Entire PC's hidden from inspector to conceal data manipulation

performing "trial" sample analysis for HPLC analyses prior to collecting the "official" analytical data

performs "unofficial testing" of samples, disregards the results, and reports results from additional tests

the running of "trial testing" prior to performing system suitability and the formal testing

QA/Manager Review Responsibilities

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No Audit Trail

Should… investigate all electronic data generated using Audit trail capabilities

HPLCs had the audit trail functions disabled

computer software lacked active audit trail functions

Switching off audit trails

loss of instrument activity logs (audit trails)

audit trail function for the chromatographic systems was disabled

QA/Manager Review Responsibilities

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Poor Review of Data and OOS

"The complete records, including failing results, are needed to carry out investigations"

failed to adequately examine why your analysts hid or deleted these runs

Your firm failed to review and investigate ..laboratory deviations

Non Contemporaneous documentation

Incorrect batch records with incorrect calculations, no signatures and missing information

Failure to investigate: customer complaints, OOS results,

QA/Manager Review Responsibilities

Poor Review of Data and OOS

You **retested analytical samples without reporting original results** in laboratory records. Because of this practice, you are **unable to assure that all raw data generated is included and evaluated** when you review analytical test results

Retest(ed) the sample on a different instrument without initiating an out-of-specification (OOS) investigation. (New..) injections were not reported as part of the original data or included in your laboratory investigation report

Details of a trial that failed impurity analysis and a follow up one that passed

Failure of Quality unit to find the errors the investigator did

your quality unit is not able to fully exercise its responsibilities.

Computer System Validation

No Validation Or Change Control

Not established and documented the accuracy, reliability and performance of your computer systems

No verification of access controls

No Validation

CSV is designed to provide documented evidence that **procedural control**, **administrative controls**, **technical controls**, are in place and configured correctly to meet user requirements.

Proper CSV would highlight

- incorrect configuration of users
- too generous abilities for roles
- opportunities for mal behaviors
- highlight areas of risk

Statements of EU Non GMP Compliance

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- **EU GMP Certificates have been publicized for some time**
  - http://eudragmdp.ema.europa.eu/inspections/gmpc/index
  - Recently opened a database of **Non Compliance Repor** (or statements of non compliance)

- **SUMMARY**
  - Deliberate falsification of results / hiding non conformities
  - Failed injections deleted
  - Discrepancies in raw data / lack of raw data
  - Inadequate review and control of computerized laboratory results and systems
  - Insufficient Qualification of Equipment
  - Quality Control deficiencies including; inadequate records, lack of specificity in analytical methods, failure to investigate unknown peaks

Summary of EU Non Conformances

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Data Manipulation	Poor Laboratory Controls	Incomplete Data Review
• Falsification of documents • **Discrepancies between electronic data and data reported on paper** • Re written training records • Falsified entries • Unreported / unauthorized trial injections of samples • Raw data chromatogram files deleted • **Retesting samples until passing results obtained**	• Failure of Lab controls • Insufficient management of data, change control and laboratory controls • No user requirements • Shared password • Failure in integrity and security of data • **Analysts routinely perform "trial" injections of sample aliquots prior to performing the official/reported analysis** • PC admin account used to **change time back and overwrite failing results** • No system validation of electronic record generating systems	• OOS results marked as Passed • **Weakness of QA department around Data integrity** • No procedure for audit trail • Hide non conformities from QA

Regulators are Focused on Data Integrity

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- Observe **ALL** data both reported and non-reported (orphan data)
  - Are the analysts **cherry picking** only the good results?
  - Are failing results being **deleted, hidden or ignored**?
    - Invalidated without justification or approval
  - Are samples being 'tested into compliance'
    - samples re-analysed /repeated until they pass or
    - manipulated by processing to ensure they pass.
- Is data secure?
  - Proper access and privileges
  - Archive, business continuity, disaster recovery
  - Is there hidden or deleted data?
- Can the story of the data be recreated?
  - Audit trails, metadata, versions

Inspection Themes

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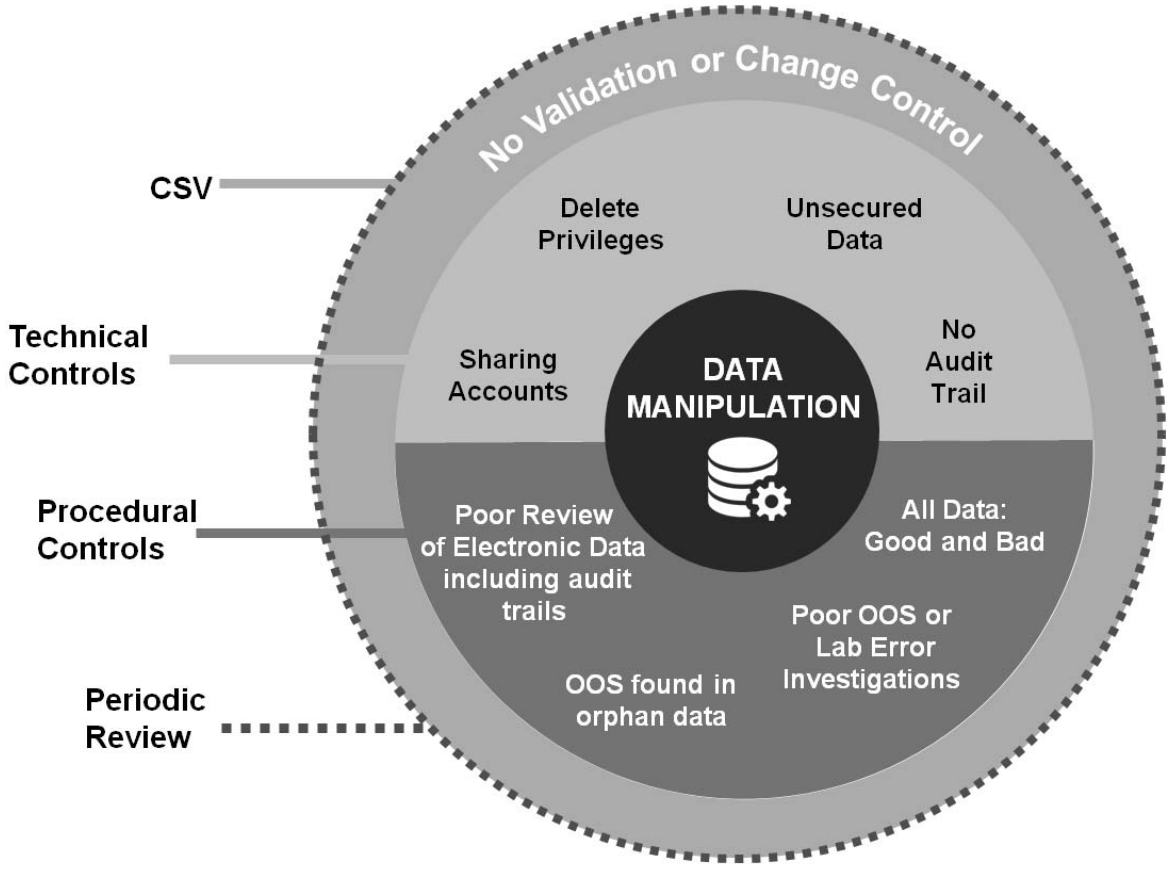

FDA Draft Data Integrity Guidance:
Rejection of Data & Repeat of Analyses

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Question 2: When is it possible to exclude cGMP data from decision making?

- Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria
  - Electronic data…should include relevant metadata

- **To exclude data….there must be a valid, documented, scientific justification for its exclusion**
  - Guidance: *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*

- The requirements for record retention and review do not differ depending on the data format;
  - Paper-based and electronic ..are subject to the same requirements.

Data Integrity and Compliance with CGMP Guidance for Industry
DRAFT April 2016

FDA U.S. FOOD & DRUG ADMINISTRATION

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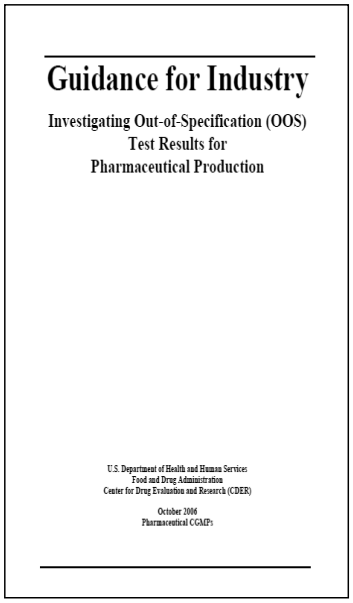
FDA Guidance on OOS and rejection of data

- "the term *OOS results includes all test results that* ***fall outside the specifications or acceptance criteria*** *..*
- *Phase I Laboratory Investigation*
  - Lab Focussed ONLY
  - Determines the validity of the result
  - Determines the root cause of potential lab error
  - 'Human Error' needs to be investigated further for true root cause
  - BEFORE any retest
  - **IOOS is now a metric asked for in the Quality Metrics initiative**

- *Phase 2 – Full Scale OOS Investigation*
  - Process AND product focussed
  - Determines the root cause of the error
  - Explores the impact on existing batches
  - Recommends corrective AND preventative actions CAPA


Guidance for Industry

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2006
Pharmaceutical CGMPs

FDA's Goal of Industry Quality Metrics Submission

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- Following a number of trials in partnership
  - with PDA and ISPE and other industry groups
- Focusing on THREE KEY Quality Metrics which they believe most closely indicate the "Quality" of an organization:
  - **Lot Acceptance Rate (LAR)**
    - Accepted lots/Lots started
  - **Product Quality Complaint Rate (PQCR)**
    - # complaints/# dosage units distributed
  - **Invalidated Out-of-Specification (OOS) Rate (IOOSR)**
    - # OOS test results for lot release and long-term stability testing due to **aberration of measurement process**/total # OOS during time period

FDA's Goal of Industry Quality Metrics Submission

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- These are metrics most companies already record for their own use
  - May be measuring or defining them differently
  - Not required to share with regulators
- **Invalidated Out-of-Specification (OOS) Rate (IOOSR)**
  - # OOS test results for lot release and long-term stability testing due to aberration of measurement process/total # OOS during time period / Number of TESTS performed on specific Sample classifications
  - In English.. # of OOS which are invalidated because of **failures in the laboratory /**

    Total number of OOS results (including real product failures) /
    Total numbers of tests performed
  - Include tests for finished product and some API testing: only
    - Lot release tests
    - Long term stability tests

FDA Draft Data Integrity Guidance:
System Suitability & Test Runs

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Question 13: Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

- FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result
  - e.g., testing different samples until the desired passing result is obtained
  - This practice, also referred to as testing into compliance is not consistent with CGMP
- We would consider it a violative practice to use an actual sample in *test, prep,* or *equilibration* runs as a means of disguising testing into compliance.
- If an actual sample is to be used for system suitability testing,
  - it should be a properly characterized secondary standard,
  - written procedures should be established and followed,
  - the sample should be from a different batch than the sample(s) being tested
  - All data should be included in the record that is retained and subject to review unless there is documented scientific justification for its exclusion

Data Integrity and Compliance with CGMP Guidance for Industry
DRAFT April 2016

U.S. FOOD & DRUG ADMINISTRATION

WHO guidance June 2016

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- System suitability runs should include **only established standards** or reference materials of known concentration to provide an appropriate comparator for the potential variability of the instrument.
- If a sample (e.g. well characterized secondary standard) is used for system suitability or trial run, written procedures should be established and followed and the results included in the data review process.
- The **article under test should not be used for trial run purposes** or to evaluate suitability of the system;

Guidance on Good Data and Record Management Practices
Released June 2016 As WHO_TRS_996 Annex 5

World Health Organization

MHRA Draft GxP guidance

- It is common for companies to overlook systems of apparent lower complexity.
- Within these systems it may be possible to **manipulate data or repeat testing** to achieve a desired outcome with limited opportunity of detection
  - (e.g. stand-alone systems with a user configurable output such as FT-IR, UV spectrophotometers).

GxP Data Integrity Definitions and Guidance for Industry
DRAFT July 2016

Orphan Data

- Data (paper or electronic) found in the laboratory (or trash bins) which is not included in final study reports/ quality certificates/ LIMS or ERP reports
- Without documented scientific reasons for its invalidation, all orphan data is suspected as
  - 'deliberately excluded to make results look better"
  - apple polishing or cherry picking
- Minimizing any failed tests or results that require repeat analysis reduces the amount of orphan data to be reviewed and addressed
- Root causes of failed tests may include:
  - Poorly developed or validated analytical methods
  - Inconsistent column separation performance
  - Sample, standard, reagent or mobile phase preparation errors
  - Instrument failures
  - Analyst error

All the data….. Is it complete? Reanalyzing into specification

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Test Injections are Good Scientific Practice

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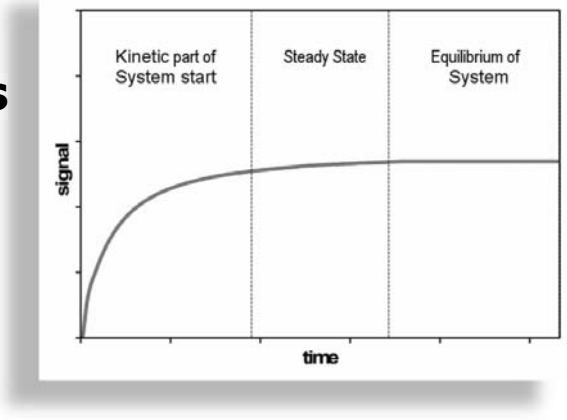
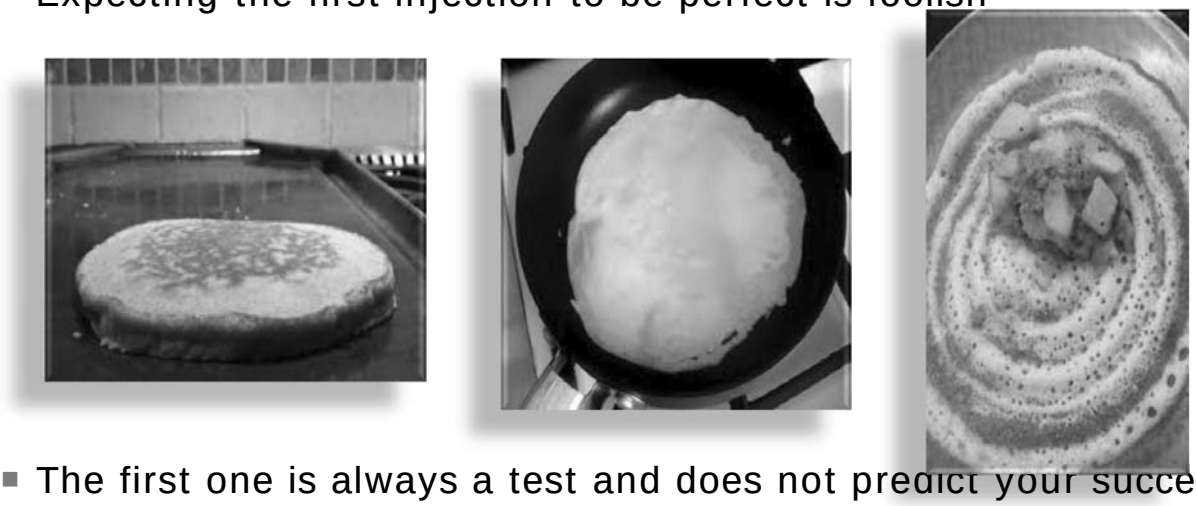
- Running any chromatography where data will be collected without first verifying that the system has been properly equilibrated is poor practice.
  - 1) Test Injections provide assurance that the system is ready and equilibrated to proceed with analysis
  - 2) Test injections verify that the column (and mobile phase combination) used can provide proper separations as this is needed in order to provide valid test results.

System Readiness Checks



Preparing a Chromatograph..

- You'll only get the correct results if your prepare the system
- You should not start the real work until you know the system is ready
- Expecting the first injection to be perfect is foolish



- The first one is always a test and does not predict your success with later attempts

Acquiring Samples SOP suggestions

- **Test Injections:** System Readiness checks
  - Never Samples, Possibly Stds
  - Preferably an independent solution which mimics real samples
    - Pooled samples?
  - Never delete them but not normal to include in reports
  - **Preventing / monitoring "Single Injections" is not an effective control**
    - **Maybe single injections.. Or short sequences**

- **System Suitability:** As part of the Sample Set/Result Set
  - If System Suitability fails… or "just" passes
    - should you continue the run?
    - Or repeat from the beginning with justification

Orphan Data

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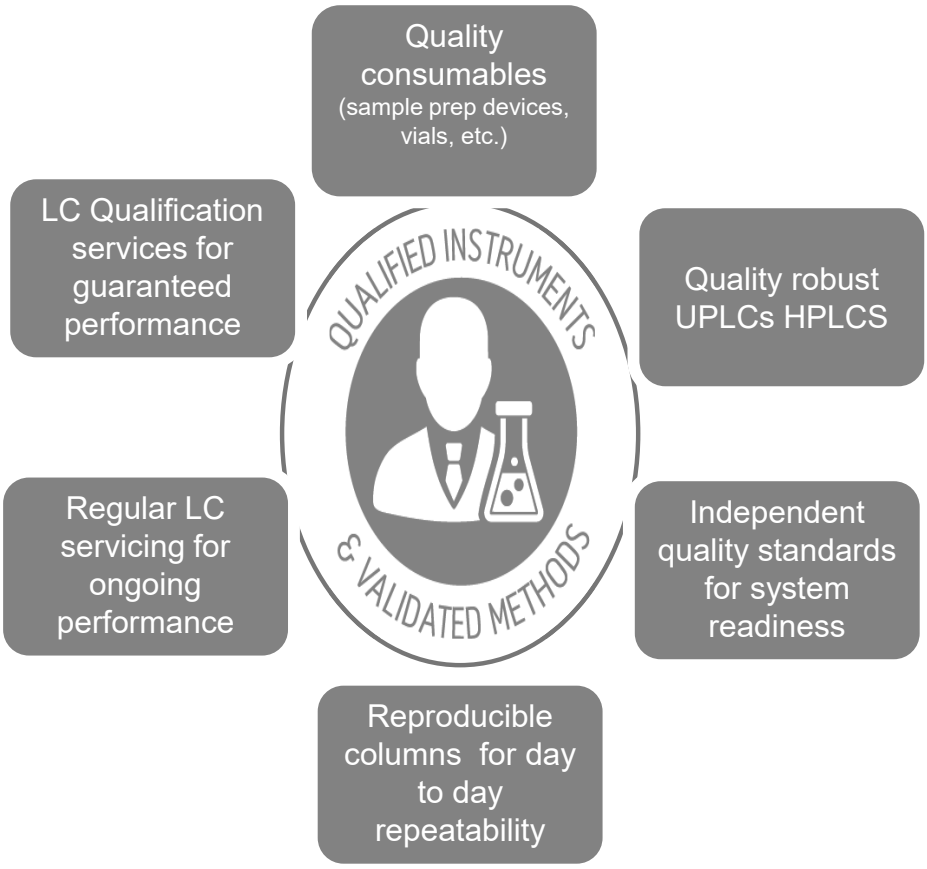
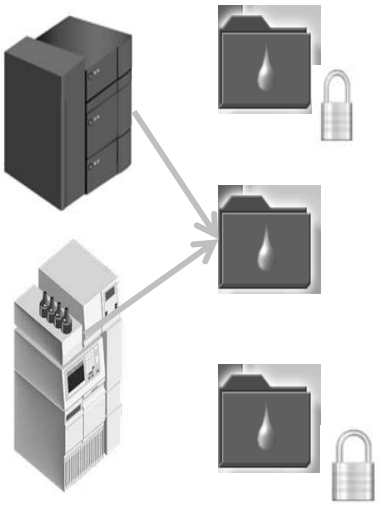
  - Analyst error

Quality Separations to Prevent Failed Results

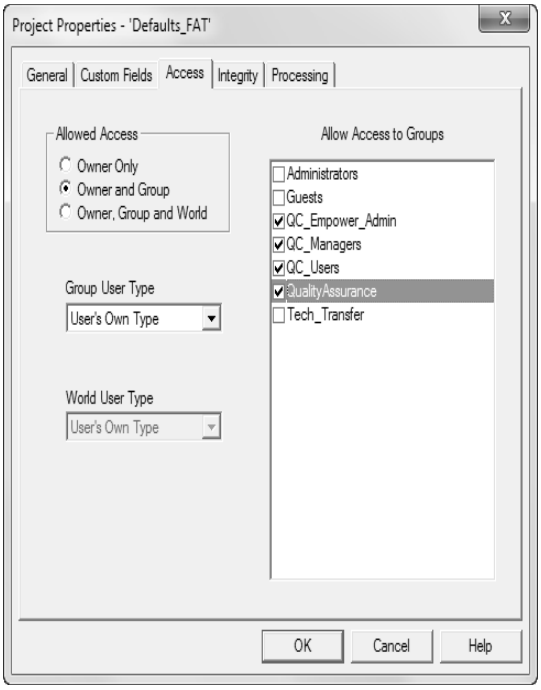


Project /Folder controls

- **Designing how projects or folders can be used is essential**
  - Only created by trained users/administrators
  - Contain all methods and calculations required for a specific test
  - Ensures that ALL data can be easily located
    - Controls user behaviour collect data in the right place
    - Assures reviewers that no data is “missing”
      - In the live CDS
      - In archives
- **Permitting users to create their own folders is a risk**
  - Ability to hide unofficial data
- **Allowing users to copy data between projects is a risk**



Project Creation and Access



Review process and procedures for project creation

Review process and procedures for project access

Other Tools:
Searching for Replicate Data

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- Empower Global Project Search
- Empower 3 Analytics
- Empower Status Report (Data Integrity Status) or EDS 365 (continuous monitoring)
  - Other Enterprise Professional Services
- Central repository
  - LIMS
  - NuGenesis LMS
- Paradigm Scientific Search
  - Searches cross Enterprise and Workstation level computers

Empower 3
Software Laboratory Analytics

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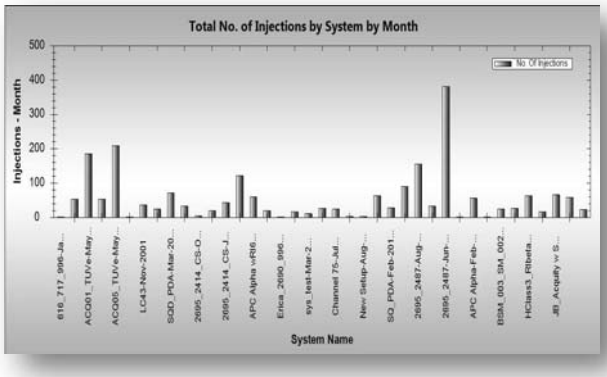
- Empower 3 Software Laboratory Analytics offers five prebuilt dashboard types:
  - System summary
  - System usage
  - Project usage analysis
  - User analysis (optional)
  - Methods analysis



Empower 3 Laboratory Analytics Allows You to:

- Access critical system usage information
- Identify training needs
- Identify error messages that affect your workflows
- Identify non-robust processing methods
- Plan for capital expenditures
- Identify opportunities to shorten run times with UPLC® technology

New in Feature Release 2

Restrict or 'Train and Review'

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Restrict	Review
▪ Limit the analysts access – To create projects – To hide data in other projects using copy – To collect data in projects other than the official one ▪ Dedicated trusted personnel and procedures for project/method creation ▪ Allow samples to be run ONLY after system suitability is demonstrated – System Readiness checks – System Suitability Testing ▪ Create a comprehensive procedure to repeat a sample or sample set analysis – Document /oversight and pre approval	▪ Review all projects for orphan raw data – 100%, before approval of 'final" results – Risk-base, by exception – Periodic or spotcheck ▪ Create a 'right sized' procedure to repeat a sample or sample set analysis – Document /oversight and pre approval ▪ Monitor methods and system performance /robustness – Improve and update as needed

FDA Draft Data Integrity Guidance:
Rejection of Data & Repeat Data Processing

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- Question 14: Is it acceptable to only save the final results from reprocessed laboratory chromatography?
- No
  - *For most lab analyses, reprocessing data should not be regularly needed.*
    - This is actually not true for Chromatography!!!
  - *If chromatography is reprocessed, written procedures must be established and followed*
    - *and **each result retained for review***
- *FDA requires complete data in laboratory records, which includes raw data, graphs, charts, and spectra from laboratory instruments*

Data Integrity and Compliance with CGMP Guidance for Industry
DRAFT April 2016

FDA U.S. FOOD & DRUG ADMINISTRATION

MHRA Draft GxP guidance

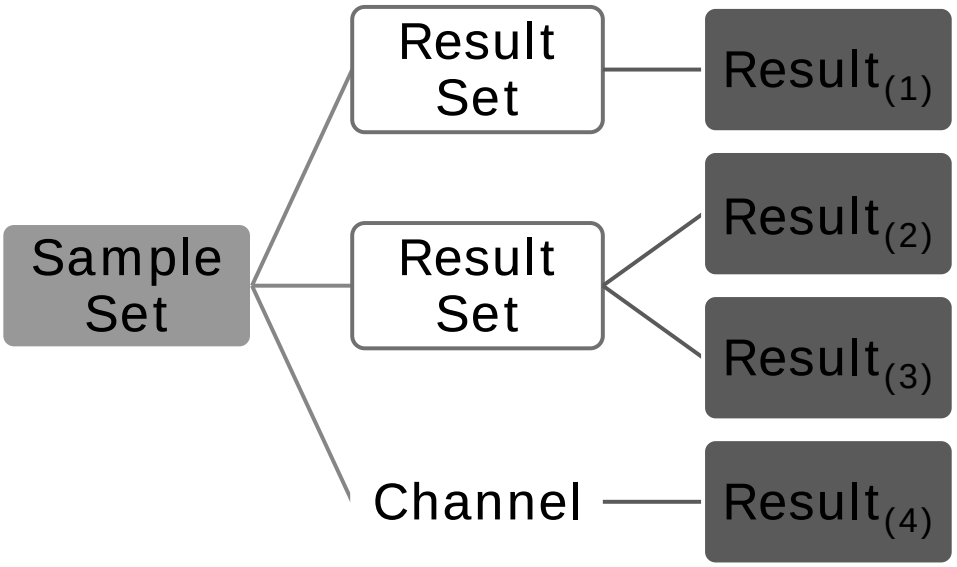
- **Data may only be excluded** where it can be demonstrated through sound science **that the data is anomalous or non representative.**
- In all cases, this **justification should be documented** and considered during data review and reporting.
- All data (even if excluded) **should be retained** with the original data set and be **available for review** in a format that allows the validity of the decision to exclude the data to be confirmed.

GxP Data Integrity Definitions and Guidance for Industry
DRAFT July 2016

Existence of Multiple Results / Channel

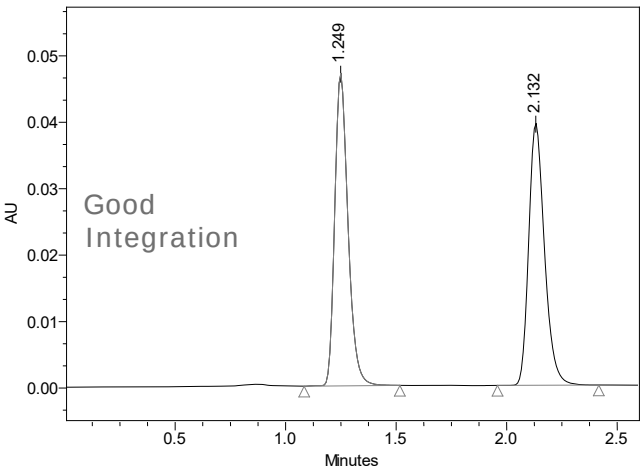
- Regulators are being trained that multiple results indicate that users are trying to reintegrate into acceptance.
- However, this conclusion can only be confirmed by looking at the actual integration for each iteration
  - Good documentation of "why" you reprocessed is essential
  - Getting it right first time, all the time, is unrealistic
    - If it data looks too good, it probably is
- Review of audit trails and all result versions are advised
- What is the "right" integration?
  - SOPs and training should define this for each method

All the data….. Is it complete?
Reprocessing into Specification



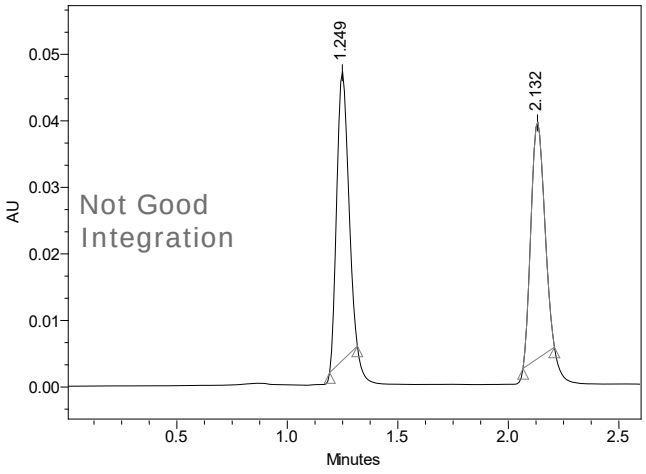
Which integration is most accurate?

Pass Fail



Manual

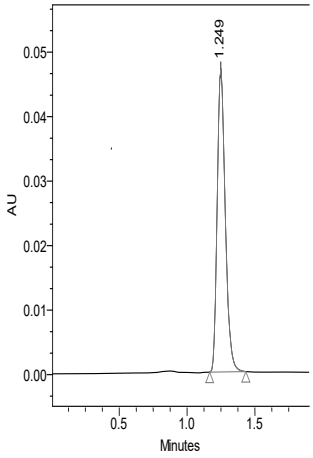
Fail Pass



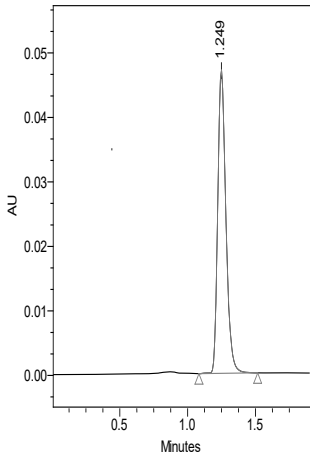
Processing Method

Manual integration isn't always bad
Automated processing methods could easily be used to manipulate integration

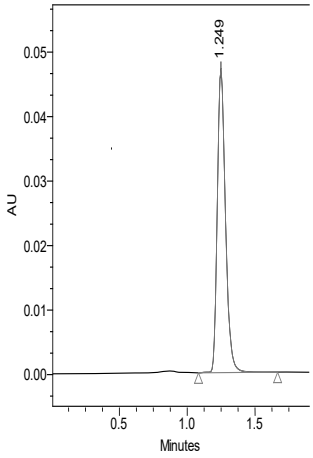
The history of integration is important



Version 1
Fail Criteria

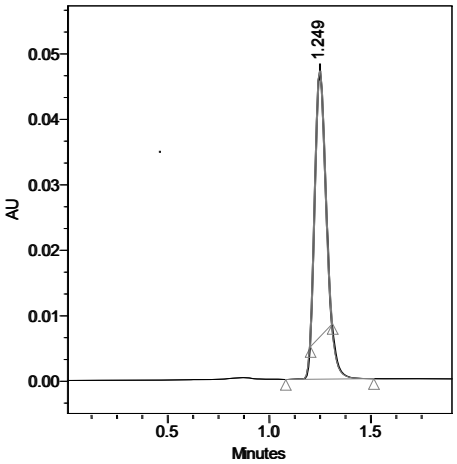


Version 2
Fail Criteria

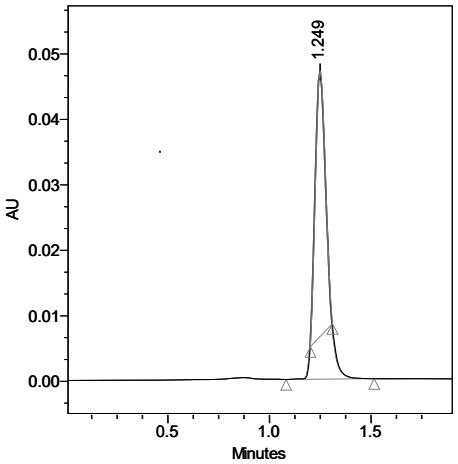


Version 3
Pass Criteria

How do I know what to review?



Version 1:
Fail Criteria



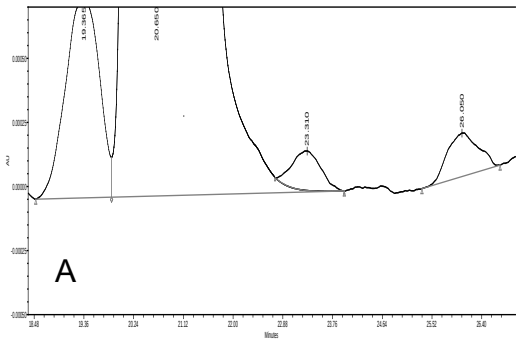
Version 36:
Pass Criteria

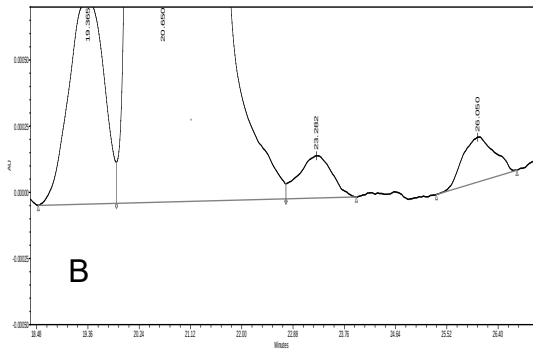
Filter By: QA Review Results

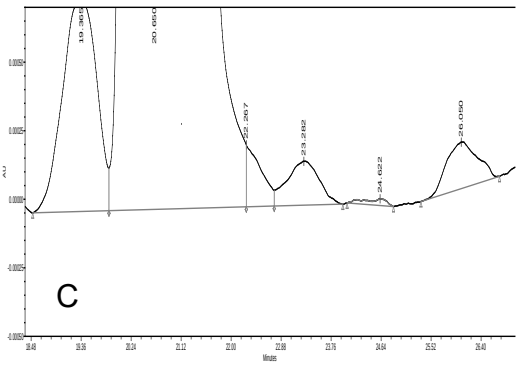
Sample Sets | Injections | Channels | Methods | Result Sets | **Results** | Peaks | Fractions | Sign Offs | Curves | View

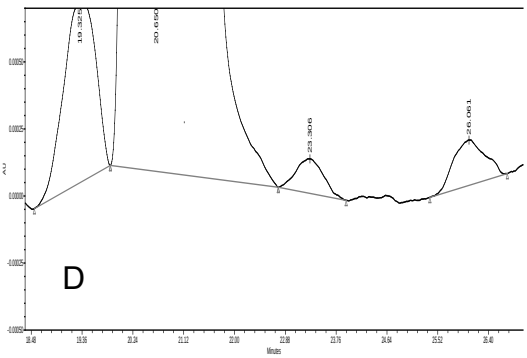
	SampleName	Vial	Injection	Sample Type	Processed Channel Descr.	# of Results Stored	Result #	Sample Set Id	Result Set Id	Result Id
1	PQ Std 10x	3	1	Standard	254nm	36	36	1103	1398	1406

What IS the right integration?

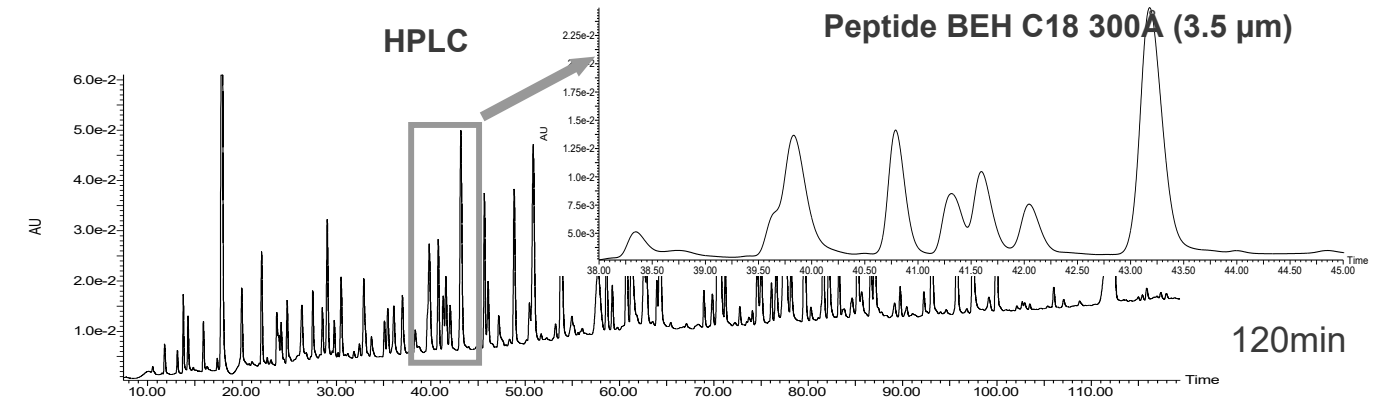


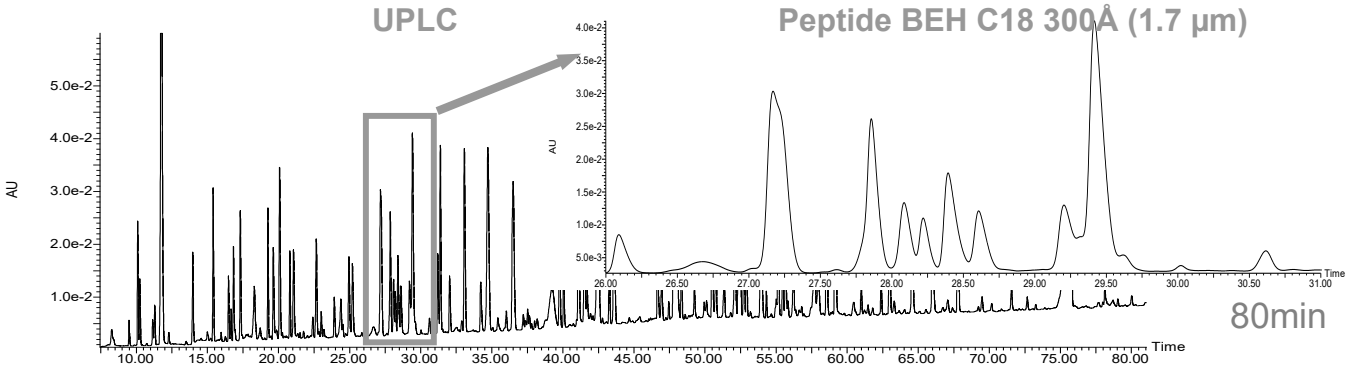






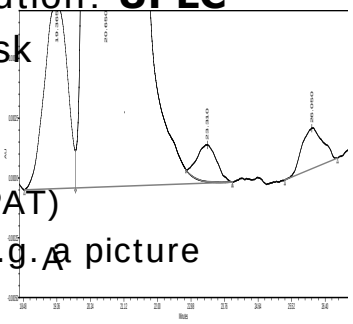
Particle Size Effect on Sensitivity and Resolution allows more robust peak integration





Avoid discussion on ‘right integration’

- Optimize method resolution to have baseline resolution: **UPLC**
- Save and review all versions of results based on risk
- Training on correct use of Integration parameters
  - Uses **Apex Track** to improve “first time right”
  - Don’t specify “parameters” specify “outcome” : (Like PAT)
  - Include example of what integration should look like e.g. a picture

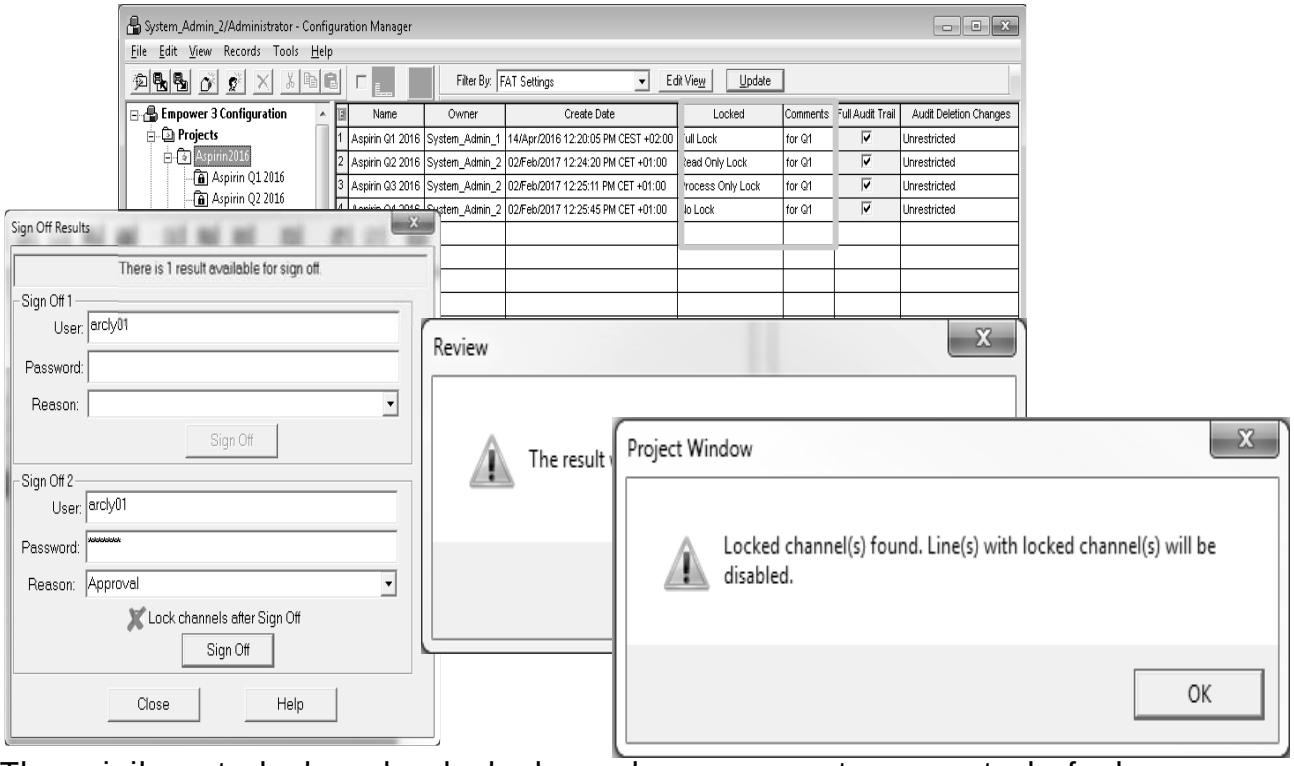


- Allow Manual Integration where required…..
  - Be sure to have an SOP and review carefully before batch release
  - Try not to force automatic integration only
- “Automatic” processing hides complex and manipulative integration methods
  - No visibility to Reviewers
  - Extremely time consuming
  - May include Manual integration by “Method”
    - E.g. force peak……

Processing Results SOP Suggestions

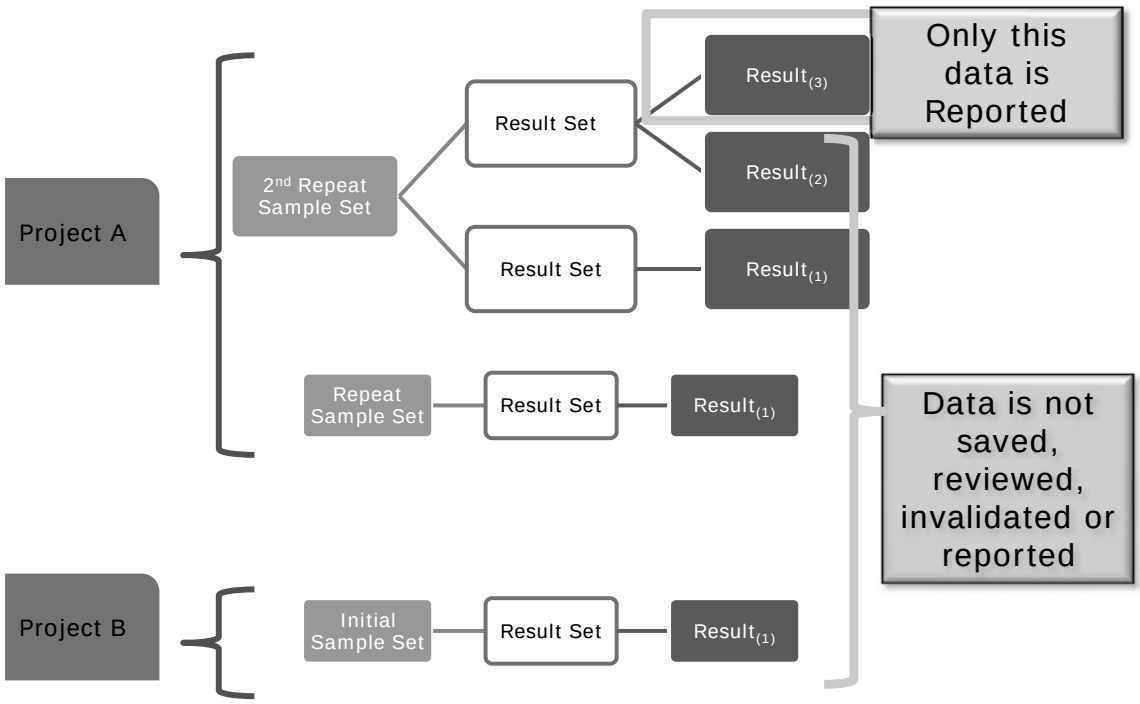
- **Same Processing parameters from top to bottom where possible**
- **Make life simple: always process in Result Sets**
  - Keeps all results together with common identifier
  - Can’t substitute or skip over individual results
  - Enforces same processing parameters
  - CAN include manual integration
    - Adds manual result into Result Set for traceability
    - Seeing both versions helps justification
- **Don’t force “right first time” integration rules (1 result per channel)**
- **Policies:**
  - **Hide “amount” fields in Review while adapting integration parameters**
  - **Prevent Calibration/Quantitation in Review**
  - **Prevent saving results from Review**

Lock Projects and Channels



The privilege to lock and unlock channels are separate so control of when results are reprocessed can be controlled.

All the data….. Is it complete?
Orphan Data



- Technical controls (project access and project creation) are important, other technical controls may not exist

Signs for DI concerns about orphan data? Or normal expected behavior

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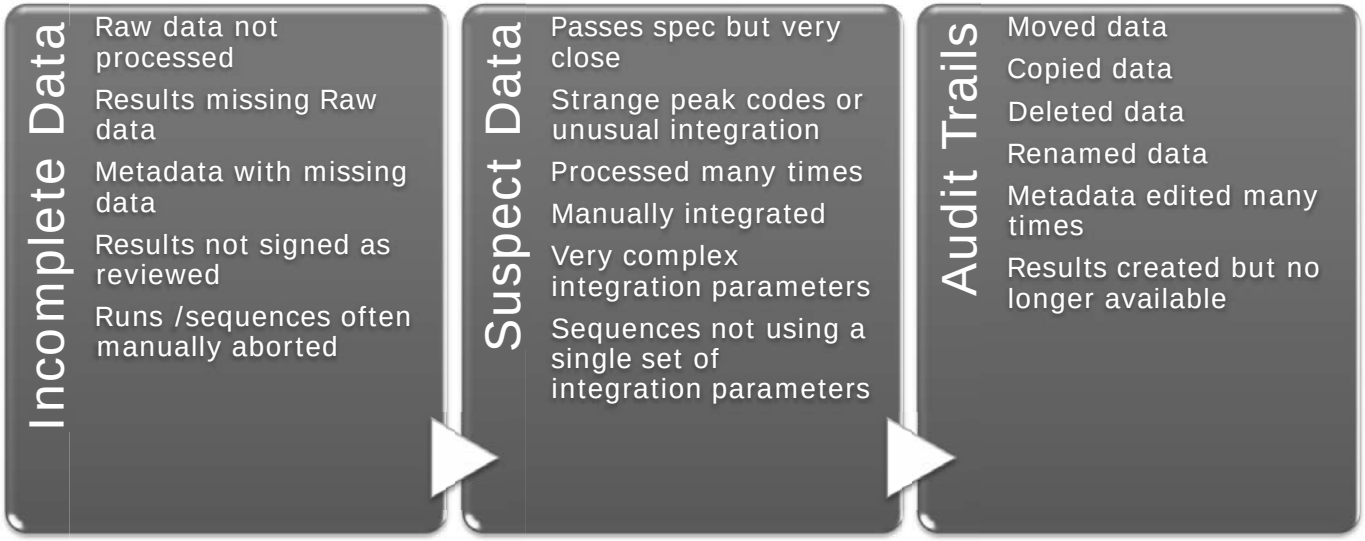

Agenda - II

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- What is Audit Trails
- Review of Audit Trails
- Make good use of
  - View as
  - View Filters
  - Results Audit Viewer
  - Empower Analytics
- Audit Trail Review Suggestions
- Examples of Audit Trails – User's Question

What is “audit trail”

- Audit trail means **a secure, computer-generated, time-stamped electronic record** that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record.
- An audit trail is a chronology of the **“who, what, when, and why”** of a record.
- For example, the audit trail for a HPLC run could include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any, including change justification for the reprocessing.

FDA Draft Guidance: Data Integrity and Compliance with CGMP (Apr 2016)

Regulatory Guidance is Changing Rapidly

PIC/S
Pharmaceutical Inspection Co-Operation Scheme

PI-041-1 (DRAFT 2), August 2016

CFDA China Food and Drug Administration

DRAFT Guidance, 2016

FDA U.S. FOOD & DRUG ADMINISTRATION

Website Q and A 2015,
DRAFT Guidance April 2016

MHRA Regulating Medicines and Medical Devices
Medicines & Healthcare Products Regulatory Agency (UK)

GMP Data Integrity, *March 2015*
‘GXP’ Data Integrity, *March 2018*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Q and A: August 2016

World Health Organization

Released June 2016,
as WHO_TRS_996 Annex 5

PDA Parenteral Drug Association

Points to Consider Series:
Conduct: March 2016
Fundamentals: Sept 2016
Data Integrity: In Progress

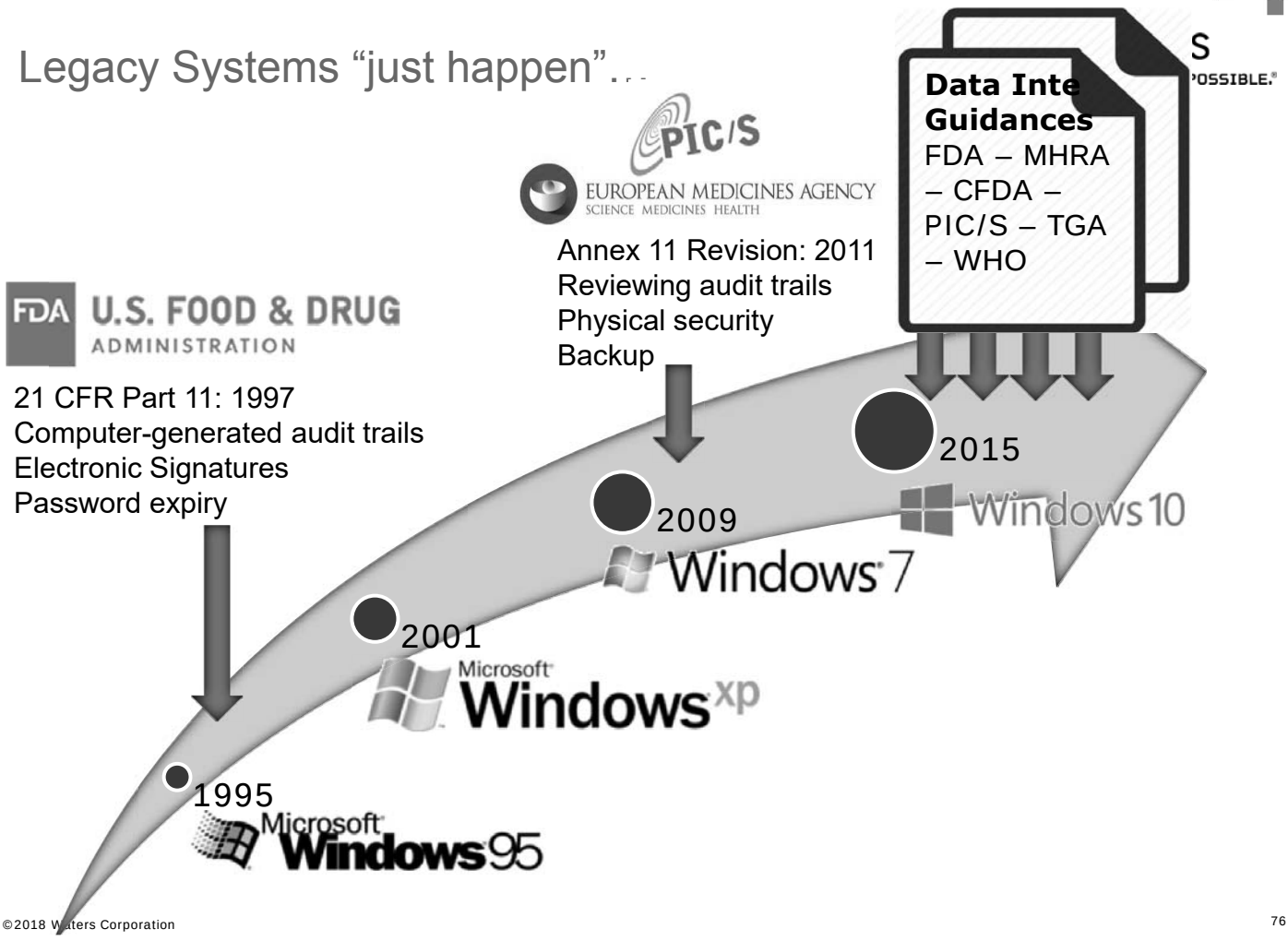
OECD

For GLP, April 2016

ISPE

GAMP: RDI Guide
Published
April 4th 2017

Legacy Systems "just happen"…



Regulatory Citations

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Examples of Non-Compliant (Legacy) Systems

- Because this instrument lacks back-up and audit trail capabilities, we could not determine how frequently test data obtained prior to "official" batch testing was discarded. *US WL 320-18-37 February 2018*
- No restricted access to the microbial identification instrument. Further, you lacked restricted access to the external hard drive used for backup of this instrument. All users could delete or modify files.
  US WL 320-17-29 March 2017
- You do not maintain electronic data on your ultraviolet-visible spectrophotometer UV SP-502 which you use for content uniformity and identity testing of **(b)(4)** capsules, and it does not have an audit trail.
  US WL 320-17-15 January 2017
- Your analyst was unable to retrieve requested data, and explained that he deletes older data to make space for newly acquired data.
  US WL 320-17-39 June 2017

Review of Audit Trails

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PIC/S

The review of data-related audit trails should be part of the routine data review within the approval process.

審閱data-related audit trails應是批准過程中例行數據審查的一部分

The regulated user should establish a SOP that describes in detail how to review audit trails.

受監管的單位應該建立SOP，詳細描述如何review audit trails

The company's Quality Unit (QU) should also review a sample of the audit trails records during the routine self-inspection.

公司的品質單位（QU）也應在例行的內部稽核時review audit trails records

Review of Audit Trails

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FDA U.S. FOOD & DRUG ADMINISTRATION

FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record. Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters.

FDA建議：對於捕獲關鍵數據變化的每個audit trails記錄都需要被審查，並在最終批准記錄之前完成審查。經過定期審閱的audit trails應包括但不限於以下內容：成品測試結果歷史記錄的變更，樣品運行順序的變化，樣品鑑別的變化以及關鍵過程參數的變化。

Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data associated with the record

負責CGMP記錄審查的人員應審查audit trails，包含重要數據更改的相關記錄

What is Data Review?

Definition:

Data review is an activity through which the correctness conditions of the data are verified. It also includes the specification of the type of the error or condition not met, and the qualification of the data and its division into the "error-free" and "erroneous" data.

Data review consists of both error detection and data analysis, and can be carried out in manual or automated mode.

http://stats.oecd.org/glossary/detail.asp?ID=3400

Data review (including second person review as required by regulation) should determine whether predefined specifications, targets, limits, or criteria have been met. The review should be based on a thorough process understanding (and where applicable system understanding) and impact on product quality and/or decision making, and outcomes and conclusion documented.

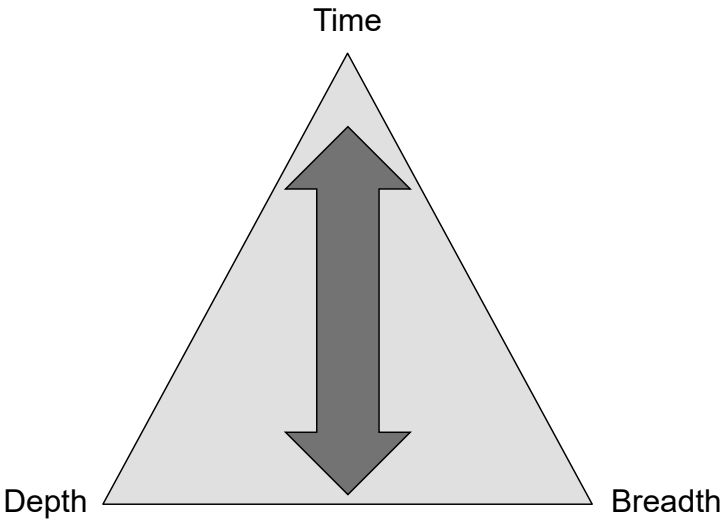
ISPE GAMP Records and Data Integrity Guide,
Section 4.4.1, Data Review

Data Review Criteria

- Each company/group need to define what criteria are needed to define the difference between a ‘good’ and a potentially ‘bad’ result…
  - Checks may include (but not be limited to)…
    - Were all samples from the same sequence or series?
    - Was the all injections processed and reported (no missing results)?
    - Has the sample been tested multiple times and/or in multiple sequences?
    - Was the correct method used for acquisition and processing?
    - Has the result been modified manually?
    - Has the sample information been altered since it was acquired?
    - Is this the latest result?
    - Has the data been processed more than once or more than a specific number of times?
    - Has the data been signed off (if you are the reviewer)?
    - Is the sample locked from further processing?
    - Are any required peaks missing?
    - Does the result ‘just pass’ its specification limits?

The Data Review Challenge

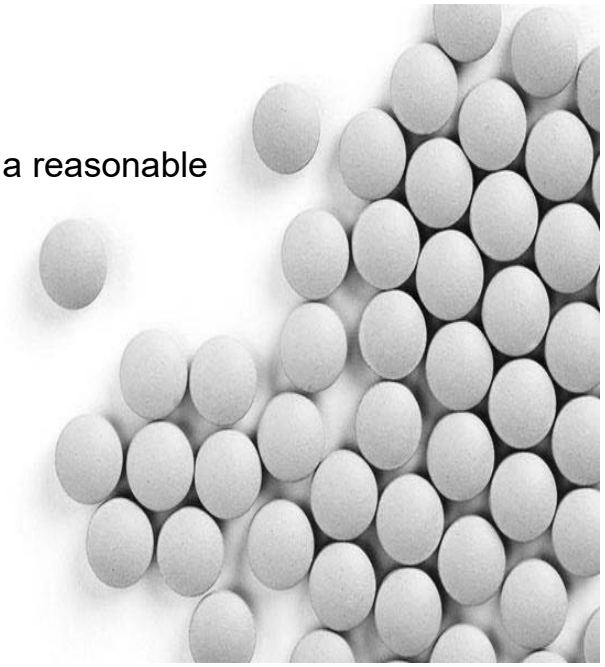
- With traditional review techniques, you cannot optimise all three key factors
  - Depth defines how many different criteria are examined for each sample
  - Breadth defines how many of the samples are examined
  - Time defines how much time is spent reviewing an individual sample



  - BUT…this is not a completely unrestricted system

Constraints on The Review Process

- Breadth of review is often defined by regulation
  - You usually must review every sample
  - Review is sample specific, so 'skipping' some samples provides no evidence of their quality or data integrity
- Review is a time-limited process
  - You must complete review for samples within a reasonable timeframe (defined by your company)



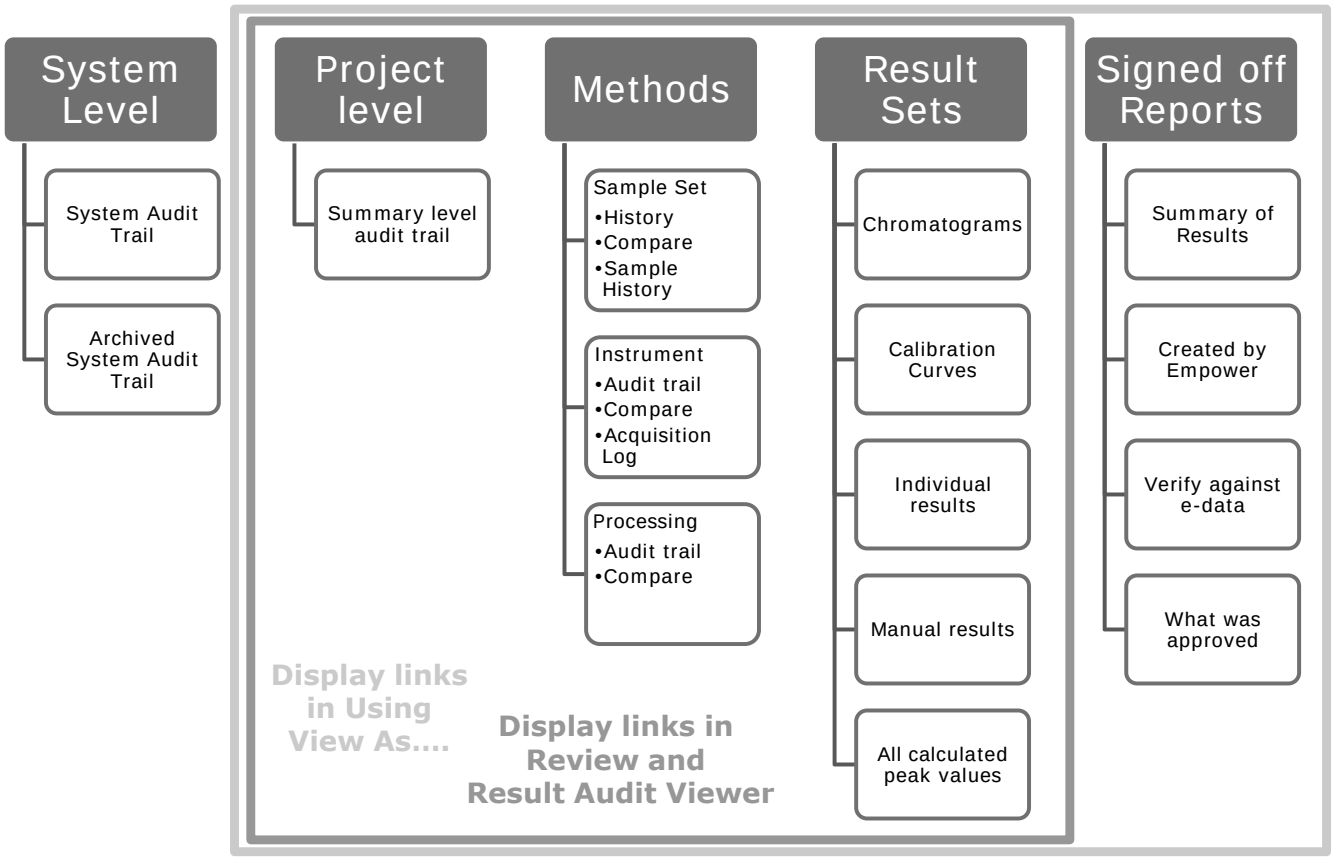
The Review Time Challenge

- An Example
  - If you need to review and release 100 samples per day, and after acquisition/processing you have 4 hours available…
    - You have 2.4 minutes available (on average) per sample if 1 person reviews all of the data
    - If a second person needs to check the initial review, you have significantly less time available per sample...assuming 1 minute for the secondary review, then you only have (at best)
      1.4 minutes to review each sample

      - Is this enough time?
      - Will quality and compliance issues be found?
      - Can the last sample be reviewed with the same ‘freshness’ as the first sample?

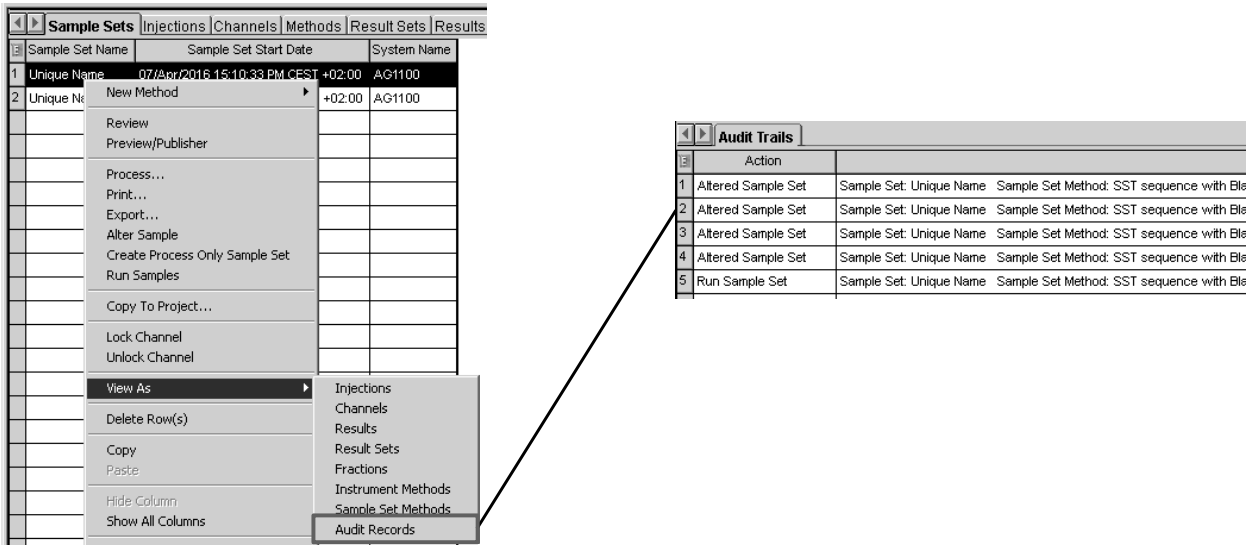
Make good use of
View As, View Filters, Result Audit Viewer, and
Empower Analytics

Empower Audit Trail Summary



"View As" Function

- It works from all tables… including view as Audit Records



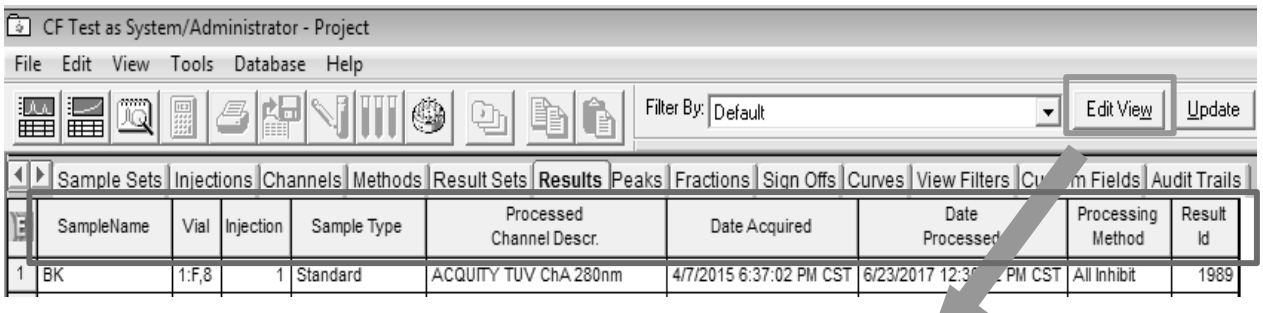
- When you want to go back to the previous view simply select
  - View as previous 
  - View as next

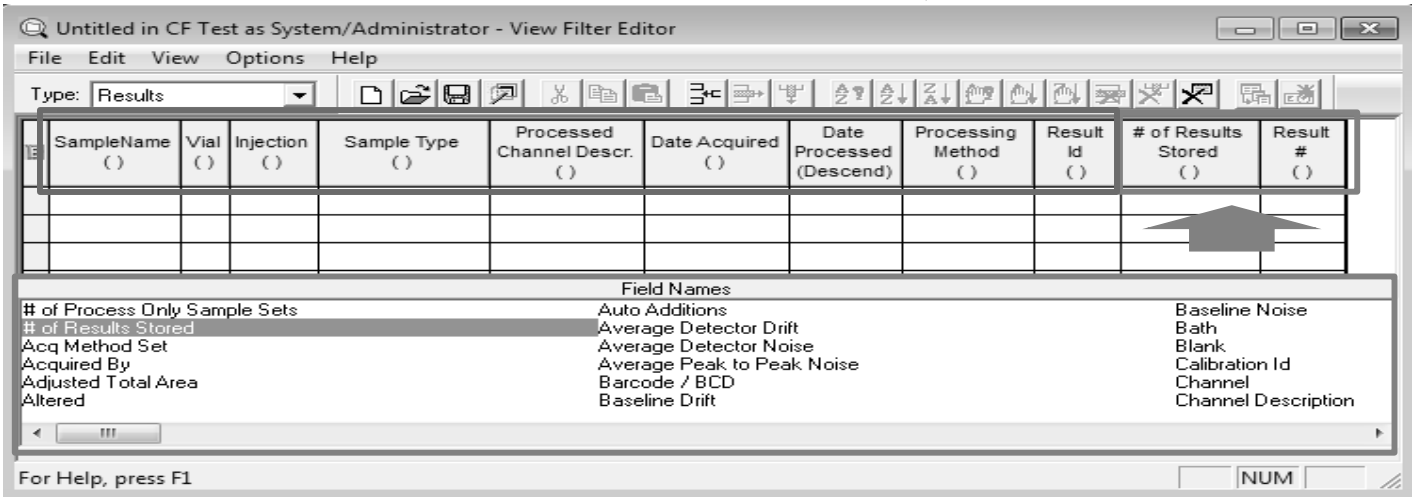
How to “View As” in Empower?

- Concerns
  - Difficult to FIND all audit records in Empower
  - Complicated SOP to follow
    - Even for experienced Empower users
    - Difficult for non/ new/ infrequent users like QA
  - No Approval of data without a report

- To see the relation between all data in an Empower project, the view as functionality is powerful
  - Sample set.. View As... Methods …then view method history
  - Result Set.. View as ...Audit Records
  - Sample Set...View as.. Results
  - Result.. View As...Sample Set …then view sample history

“View Filter” Function

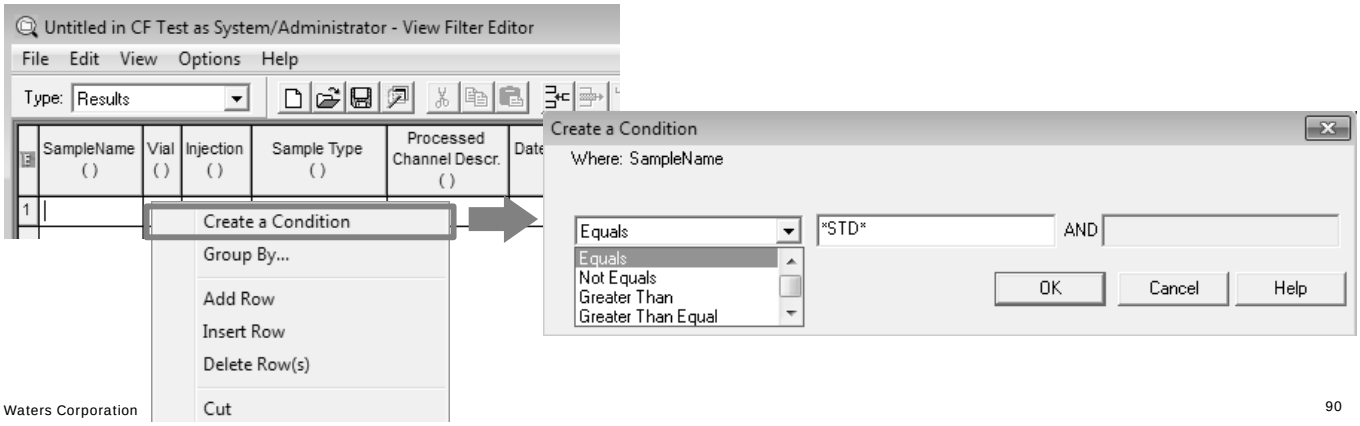




“View Filter” Function

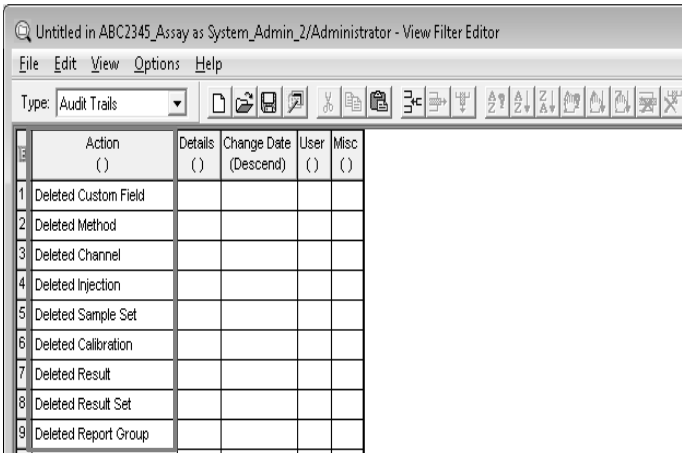
- Check the information of the fields – “Result” table as an example :
  - 「# of Result Stored」、「Result #」、「Result Source」
  - 「Result ID」、「Instrument Method ID」、「Processing Method ID」 「Sample Set ID」、「Calibration Curve ID」
  - 「Comments」、「Sample Set Comments」、「Result Comments」
  - 「Alter」、「Manual」、「Fault」、「Number of Sign Offs」
  - 「Acquired By」、「Processed By」、「System Name」

- Set View Filter conditions



View Filter | Check for deletion actions within Project Audit Trail

- Check Project Audit Trail for any Deletion



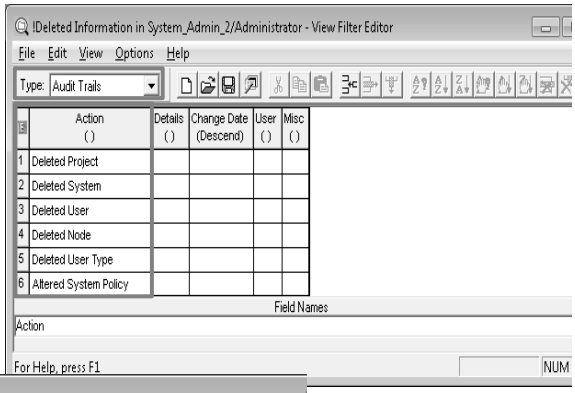
  - In project Audit Trail view, create filter, including all the deletion actions.
  - Update the view to show the actions involving deletion

Sample Sets | Injections | Channels | Methods | Result Sets | Results | Peaks | Fractions | Sign Offs | Curves | View Filters | Custom Fields

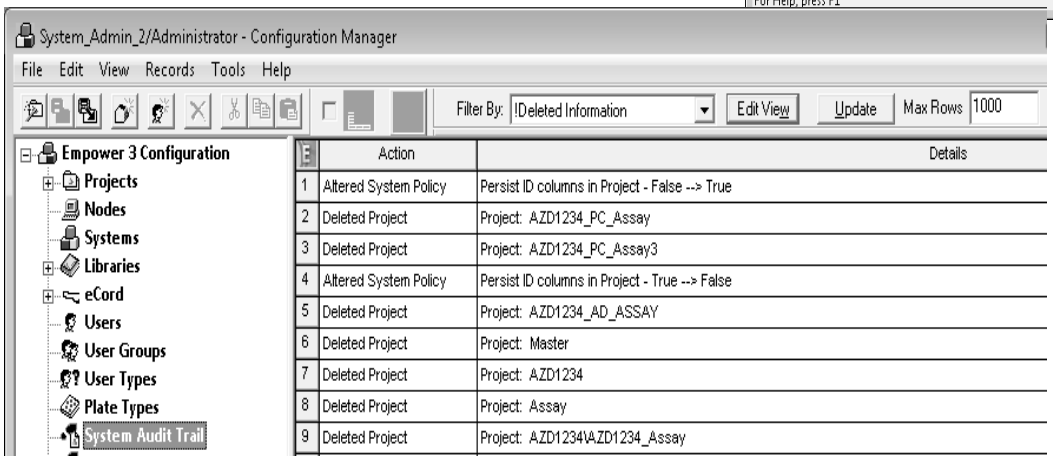
	Action	Details	Ch
1	Deleted Method	Method: 3 samples bracketted Type: Sample Set Version: 1 Reason: for deletion after incorrect creation	12/Jun/2017 21
2	Deleted Method	Method: PaulF Type: Sample Set Version: 3 Reason: for deletion after incorrect creation	12/Jun/2017 21
3	Deleted Method	Method: PaulF_Screening Type: Sample Set Version: 2 Reason: for deletion after incorrect creation	12/Jun/2017 21

View Filter | Check for deletion actions within System Audit Trail

- To check for deleted information at system level
  - In Audit Trails view, create filter including all the deletion actions and changes to system policies



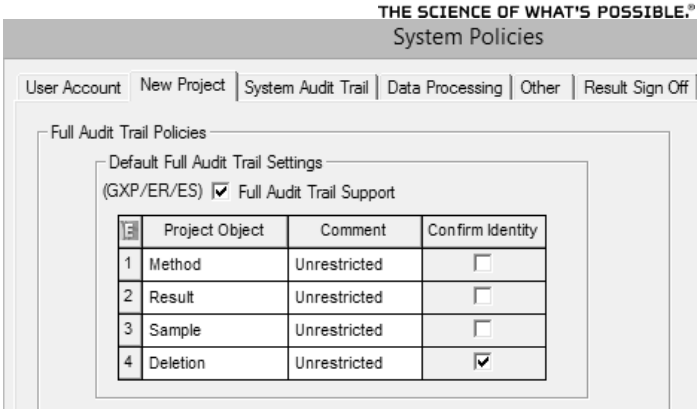
  - Update the view to show those actions



View Filter | System Audit Trail - FAT Settings of Projects

- Click Edit View on the Project View, and add the following 8 columns to the view.

Audit Deletion Changes
Audit Deletion Confirm Identity
Audit Method Changes
Audit Method Confirm Identity
Audit Result Changes
Audit Result Confirm Identity
Audit Sample Changes
Audit Sample Confirm Identity



- Save the View Filter and Apply
- Now for each of the projects the FAT settings are shown

Name	Owner	Locked	Comments	Full Audit Trail	Audit Deletion Changes	Audit Deletion Confirm Identity	Audit Method Changes	Audit Method Confirm Identity	Audit Result Changes	Audit Result Confirm Identity	Audit Sample Changes	Audit Sample Confirm Identity
Defaults_FAT	System	No Lock	Default project	☑	Unrestricted	☑	Unrestricted	☐	Unrestricted	☐	Silent	☐
Installation Testing	System	No Lock	for checking the initial settings	☑	Unrestricted	☑	Unrestricted	☐	Unrestricted	☐	Silent	☐
Manual Integration	System	No Lock	for manual integration of peaks	☑	Unrestricted	☑	Silent	☐	Silent	☐	Silent	☐
Master 1	System	No Lock	for legacy fields	☑	Unrestricted	☑	Silent	☐	Silent	☐	Silent	☐
Master 2	System	No Lock	for legacy fields	☑	Unrestricted	☑	Silent	☐	Silent	☐	Silent	☐
Master 3	System	No Lock	for legacy fields	☑	Unrestricted	☑	Silent	☐	Silent	☐	Silent	☐
Master 4	System	No Lock	for legacy fields	☑	Unrestricted	☑	Silent	☐	Silent	☐	Silent	☐
Master RnD	System	No Lock	for R&D work	☑	Silent	☑	Silent	☐	Silent	☐	Silent	☐
Res_Product 1 16Q1	System	Read Only Lock	for compound XYZ	☑	Unrestricted	☑	Unrestricted	☐	Unrestricted	☐	Unrestricted	☐

US Warning Letter WL:320-14-03

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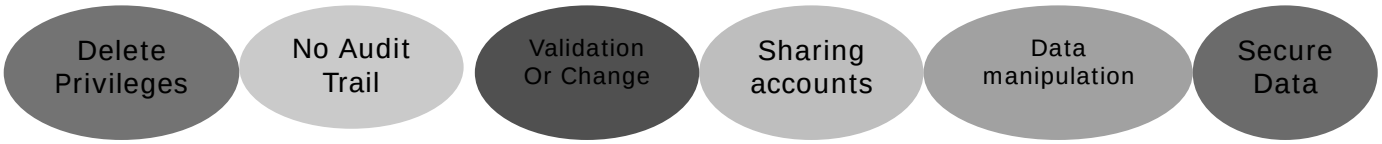
> Your firm failed to have adequate procedures for the use of computerized systems in the quality control (QC) laboratory. Our inspection team found that current computer users in the laboratory were able to delete data from analyses. Notably, we also found that the audit trail function for the gas chromatograph (GC) and the X-Ray Diffraction (XRD) systems was disabled at the time of the inspection. Therefore, your firm lacks records for the acquisition, or modification, of laboratory data.

- Shared Log in accounts
- Switching off audit trails
- Users can delete data
- Making balance printouts retrospectively after chromatographic runs were made
- No backups
- No verification of access controls
- No Validation
- They were advised to get a data integrity consultant to help them determine the extent of the data issue both currently as well as historically, including interviewing ex employees.



Result Audit Viewer Tool

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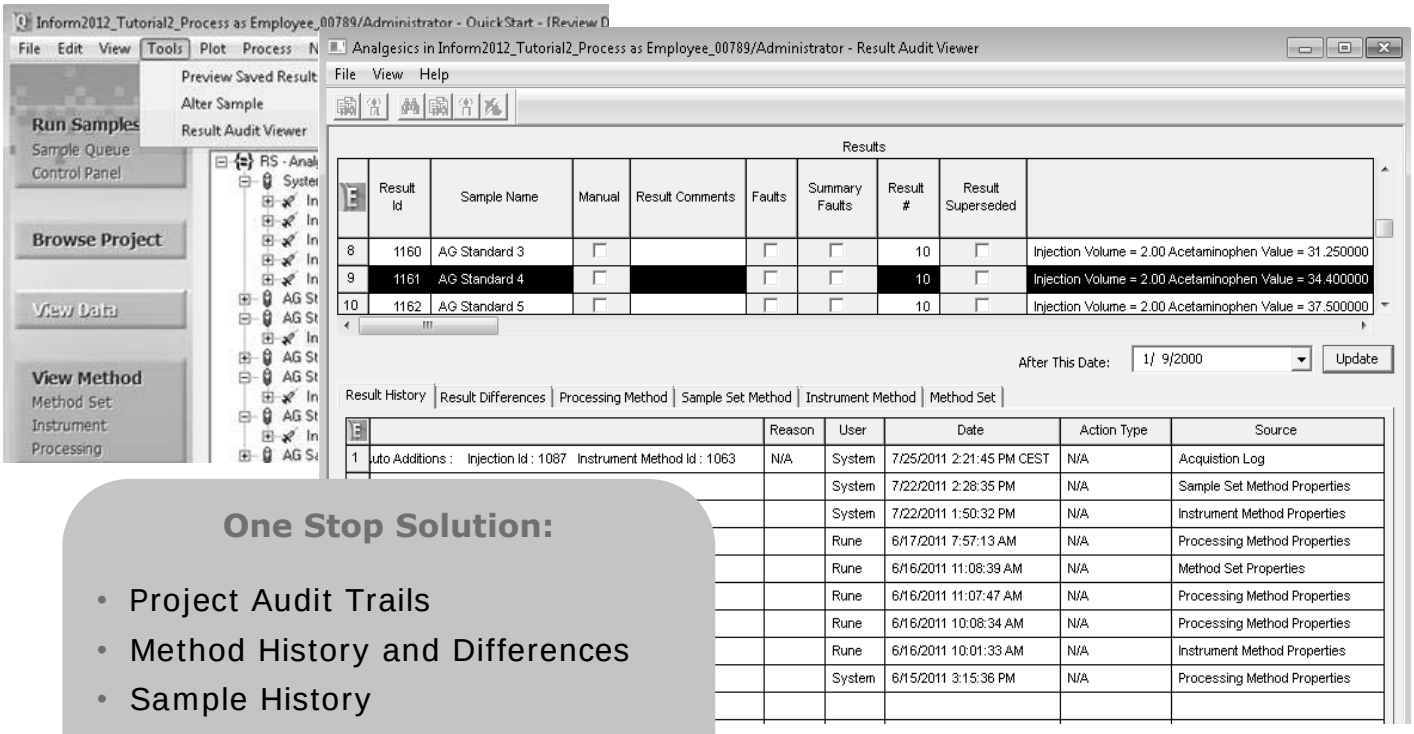


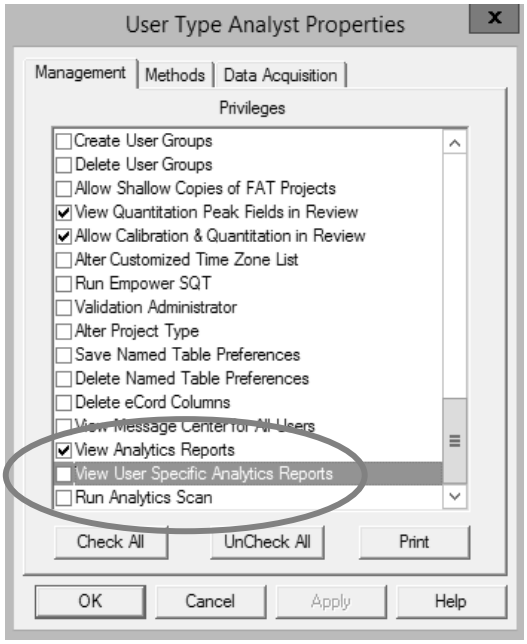
One Stop Solution:

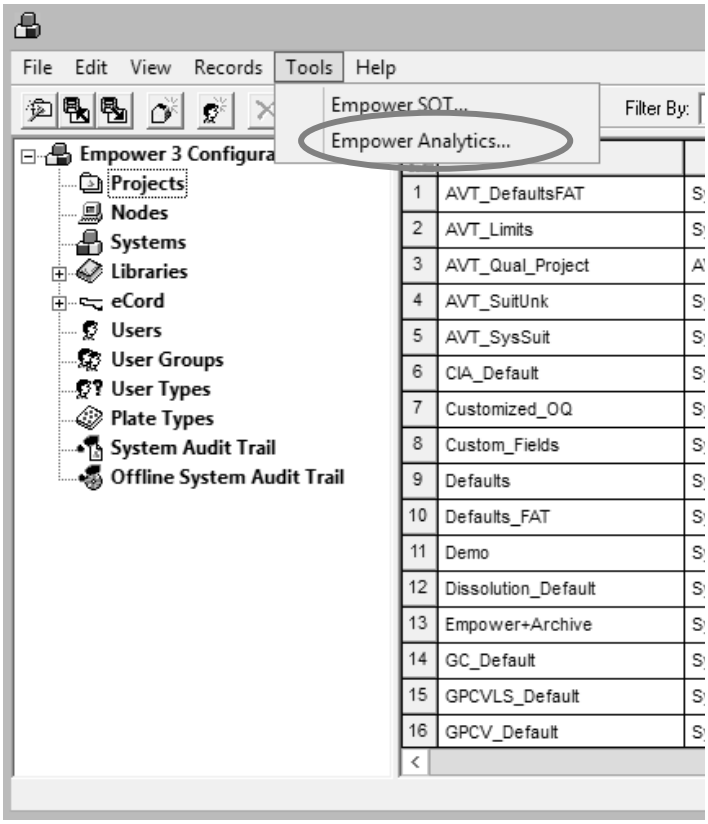
- Project Audit Trails
- Method History and Differences
- Sample History
- Sample Set History
- Acquisition Log
- Injection Log

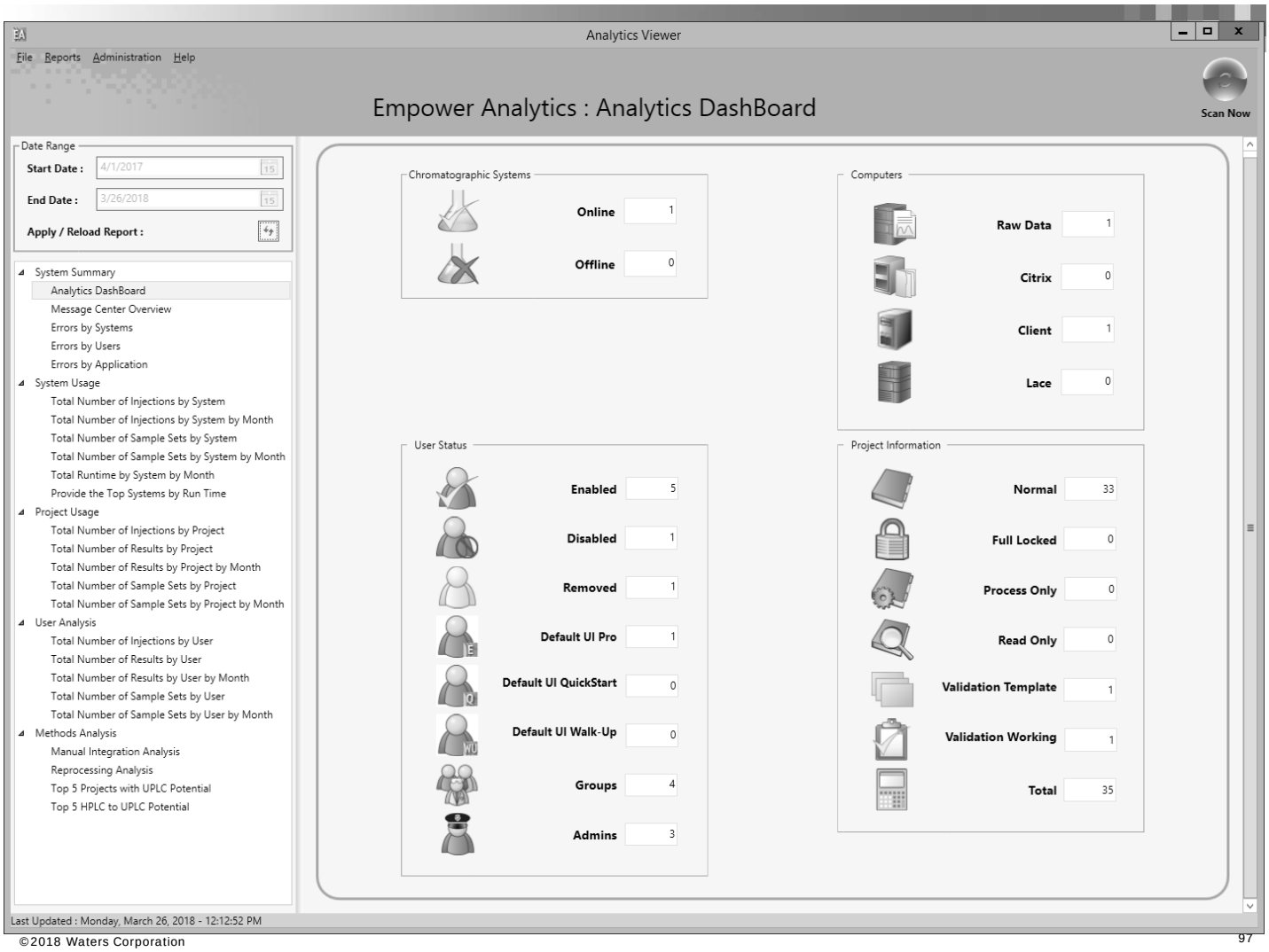
New in Empower 3 FR 2

What is Empower Analytics?

- Included in Empower base licence
- Privileges can be set to control who can access / run Analytics scan







What's interesting for Data Integrity?

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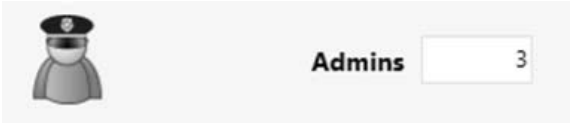
- How many full administrators?



- US Warning Letter WL:320-17-25

"Your response states that your SOP for electronic data management specifies that only information technology staff will have full administrator rights. However, you did not specify which information technology personnel will have these administrator rights. In addition, this SOP became effective on May 9, 2016, prior to the FDA inspection. However, your quality control management still had full administrative rights to all computerized systems during our inspection from May 30 to June 1, 2016."

- Are there any suspicious projects?

Project Name	Injections
CIA_Default	22
Customized_OQ	15
GPCVLS_Default	17
WASH	3353
AVT_Qual_Project	1

- US Warning Letter WL:320-15-06:

"found a data folder entitled "WASH"… One of your laboratory analysts stated that this folder does not contain any standard or sample injection results. However, our investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples."

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Audit Trail Suggestions

Risk-Based Approach to Review

- Review all data equally
  - Takes a lot of time
  - Still not enough to detect DI issues

- Risk-based review
  - Determine what are best indicators for records at risk
    - Re-processing
    - Altered sample
    - Results just within specification
    - …….
  - Create view filters to find those records
    - Focus time and effort on reviewing previous integrations, result audit trail, sample prep data etc.
- More likely to detect DI issues

Data Review SOP Suggestions

- Should be performed on ELECTRONIC data in the application at least at Peer Review level
  - Not relying on paper /pdf or Empower reports entirely
- Define a Process
  - Start at either the end result and work backwards to acquisition
  - Or start at acquisition and work towards the result
- Look at final results (summaries, averages, CofA)
  - Work back through the data from final quantitation, to areas and integration to SampleSet meta data to audit trails
  - Specifically focus on suspect data
    - Define a list of warning signs..
      - Manual integration / multiple results / metadata changes
      - Results that only just meet specification

How to document Data Review including Audit Trails

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- Review chromatograms, methods and relevant Audit Trails electronically in the computerised system
- Document that process by SIGNATURE
  - Sign a report to document that you have followed the review SOP

I sign this data to attest that I performed/ reviewed / approved this data according to SOP 12345

SOP should document what to review and how it should be done by your role

- Similar to other laboratory tasks where there is no proof of the activity (such as making mobile phases or sample preparation) other than a user attesting to their completion of the task

Review by Exception – Using Reports to Make Review and Decision Making Simpler

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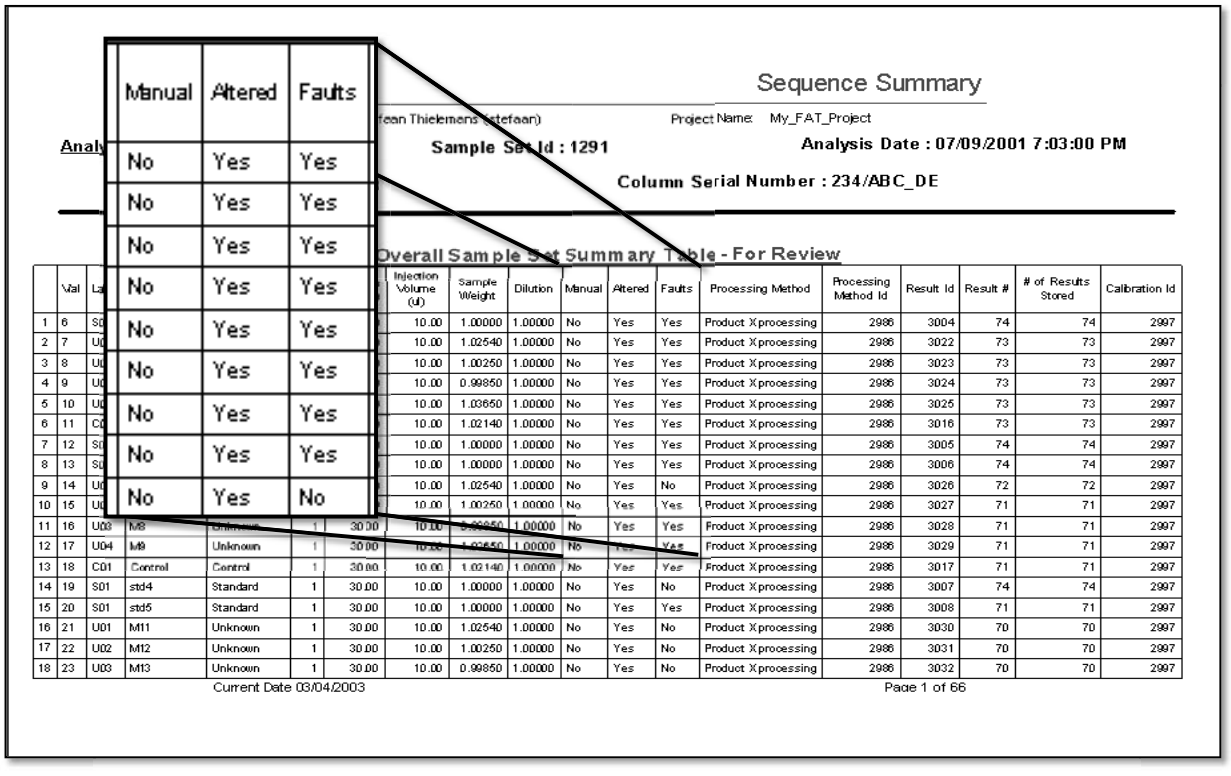
- Summary reports to point to areas of highest risk



Manual	Altered	Faults
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	Yes
No	Yes	No

Sequence Summary

Project Name: My_FAT_Project

Sample Set Id : 1291

Analysis Date : 07/09/2001 7:03:00 PM

Column Serial Number : 234/ABC_DE

Overall Sample Set Summary Table - For Review

	Val	La				Injection Volume (ul)	Sample Weight	Dilution	Manual	Altered	Faults	Processing Method	Processing Method Id	Result Id	Result #	# of Results Stored	Calibration Id
1	6	S0				10.00	1.00000	1.00000	No	Yes	Yes	Product Xprocessing	2986	3004	74	74	2997
2	7	U0				10.00	1.02540	1.00000	No	Yes	Yes	Product Xprocessing	2986	3022	73	73	2997
3	8	U0				10.00	1.00250	1.00000	No	Yes	Yes	Product Xprocessing	2986	3023	73	73	2997
4	9	U0				10.00	0.99850	1.00000	No	Yes	Yes	Product Xprocessing	2986	3024	73	73	2997
5	10	U0				10.00	1.03650	1.00000	No	Yes	Yes	Product Xprocessing	2986	3025	73	73	2997
6	11	C0				10.00	1.02140	1.00000	No	Yes	Yes	Product Xprocessing	2986	3016	73	73	2997
7	12	S0				10.00	1.00000	1.00000	No	Yes	Yes	Product Xprocessing	2986	3005	74	74	2997
8	13	S0				10.00	1.00000	1.00000	No	Yes	Yes	Product Xprocessing	2986	3006	74	74	2997
9	14	U0				10.00	1.02540	1.00000	No	Yes	No	Product Xprocessing	2986	3026	72	72	2997
10	15	U0				10.00	1.00250	1.00000	No	Yes	Yes	Product Xprocessing	2986	3027	71	71	2997
11	16	U03	M8	Unknown	1	30.00	10.00	0.99850	1.00000	No	Yes	Yes	Product Xprocessing	2986	3028	71	71	2997
12	17	U04	M9	Unknown	1	30.00	10.00	1.03650	1.00000	No	Yes	Yes	Product Xprocessing	2986	3029	71	71	2997
13	18	C01	Control	Control	1	30.00	10.00	1.02140	1.00000	No	Yes	Yes	Product Xprocessing	2986	3017	71	71	2997
14	19	S01	std4	Standard	1	30.00	10.00	1.00000	1.00000	No	Yes	No	Product Xprocessing	2986	3007	74	74	2997
15	20	S01	std5	Standard	1	30.00	10.00	1.00000	1.00000	No	Yes	Yes	Product Xprocessing	2986	3008	71	71	2997
16	21	U01	M11	Unknown	1	30.00	10.00	1.02540	1.00000	No	Yes	No	Product Xprocessing	2986	3030	70	70	2997
17	22	U02	M12	Unknown	1	30.00	10.00	1.00250	1.00000	No	Yes	No	Product Xprocessing	2986	3031	70	70	2997
18	23	U03	M13	Unknown	1	30.00	10.00	0.99850	1.00000	No	Yes	No	Product Xprocessing	2986	3032	70	70	2997

Current Date 03/04/2003

Page 1 of 66

Can Review Be Automated?

MHRA
Regulating Medicines and Medical Devices

- Routine data review should include a documented audit trail review
- Could be through an **exception report**.. abnormal data which requires further attention or investigation

PIC/S

- Where data summaries are used for internal or external reporting, evidence should be available to demonstrate that such summaries have been verified in accordance with raw data.
- **Exception report**: A validated search tool that identifies and documents predetermined 'abnormal' data or actions, which requires further attention or investigation by the data reviewer.

World Health Organization

- "Systems may be designed to facilitate audit trail review by various means; for example, the system design may permit audit trails to be reviewed as a list of relevant data or by a validated **exception reporting process**"

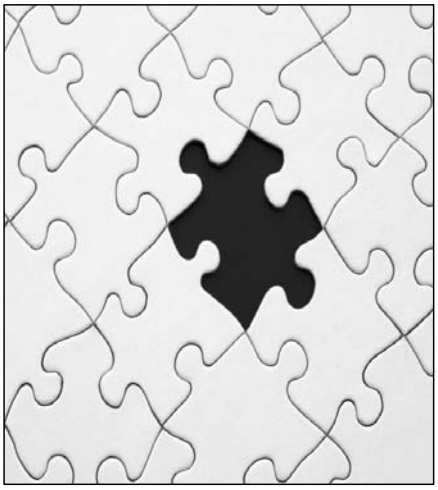
Enhancing the Review Process

- By using all the previous information stored in the Empower database, we can streamline review considerably

	SampleName	Result Id	Sample Set Id	Instrument Method Id	Processing Method Id	Altered	Faults	Manual	Processing Locked	# of Results Stored	Result #
1	PQ Std. 2.5x	1037	1002	1004	1010	☑	☐	☐	☐	1	1
2	PQ Std 5.0x	1038	1002	1004	1010	☑	☐	☐	☐	1	1
3	PQ Std 10x	1039	1002	1004	1010	☑	☐	☐	☐	1	1
4	PQ Unk. 1	1040	1002	1004	1010	☑	☐	☐	☐	1	1
5	PQ Unk. 2	1041	1002	1004	1010	☑	☐	☐	☐	1	1
6	PQ Unk. 3	1042	1002	1004	1010	☑	☐	☐	☐	1	1
7	PQ Unk. 4	1043	1002	1004	1010	⚠☑	☐	☐	☐	1	1

Enhancing the Review Process

- What is Still Missing?
  - An exception summary table still requires manual interpretation but is faster and less error prone than fully manual review
    - Could still miss some values in large sample runs
    - Still requires reference to SOP's and method parameters
  - Does not answer the following questions
    - Was all injections processed and reported (no missing results)?
    - Has the sample been tested multiple times and/or in multiple sequences?
    - Does the result fail, or 'just pass', its product specification limits?

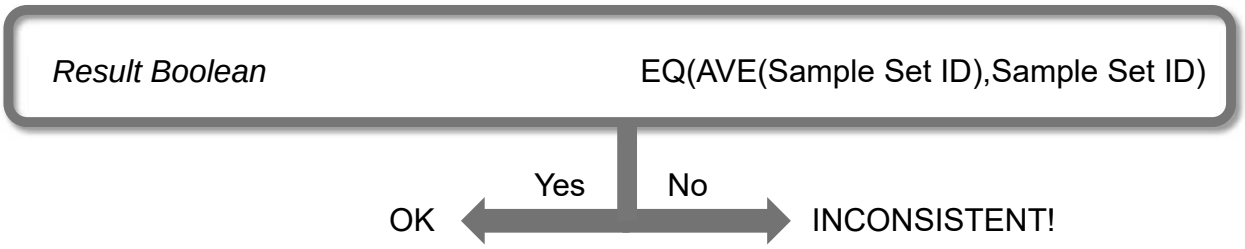


Further Automating the Review Process

- Custom fields can be used to calculate and determine almost all requirements for data review
  - Using boolean (or enumerated) calculations to determine good from bad, or one of a range of possibilities
    - Make it simpler to interpret for the user
  - Use intersample calculations to determine the consistency of a set of data
    - Remove the need to scan large number of entries
  - Use the 'CConst' fields in the processing method to define compound specific values that should not be changed
    - Prevent the analyst changing sensitive values and remove the need for data entry
    - Update values in the method if the product specification changes
  - Database ID's are critical to identify versions

How Can We Automate…

- Were all samples from the same sequence or series?
  - Empower identifies everything run together using a ‘SampleSet ID’ that is maintained in the database
  - If the Sample Set ID for the result is the same for every sample being processed, then the sequence is the same/consistent.

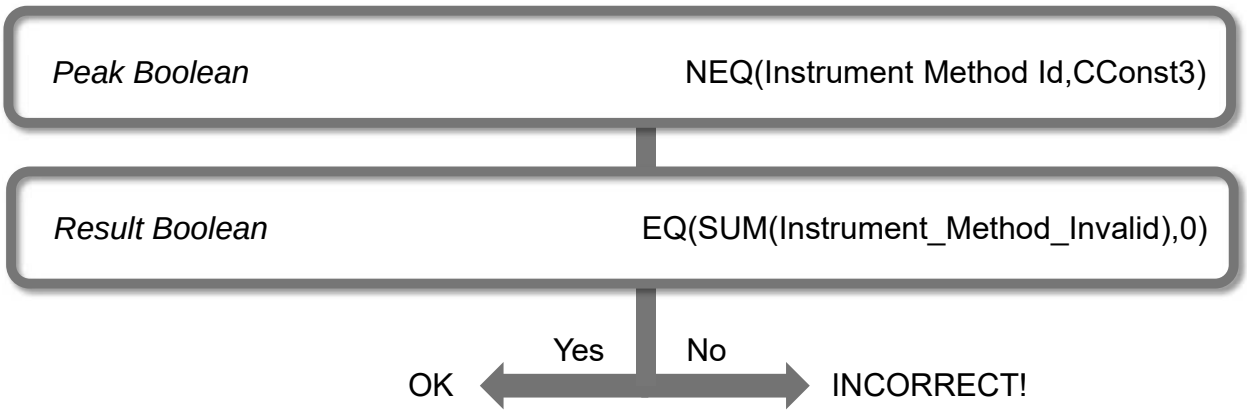


	SampleName	Result Id	Sample Set Id	Sample_Sequence_Consistent
1	PQ Std. 2.5x	1180	1002	OK
2	PQ Std 5.0x	1181	1002	OK
3	PQ Std 10x	1182	1002	OK
4	PQ Unk. 1	1183	1002	OK

	SampleName	Result Id	Sample Set Id	Sample_Sequence_Consistent
1	PQ Std. 2.5x	1180	1002	INCONSISTENT
2	PQ Std 5.0x	1181	1002	INCONSISTENT
3	PQ Std 10x	1182	1031	INCONSISTENT
4	PQ Unk. 1	1183	1002	INCONSISTENT

How Can We Review…

- Was the correct method used for acquisition and processing?
  - Store the required method ID to be used in a CConst field in the processing method (cannot work for the Processing Method itself!)

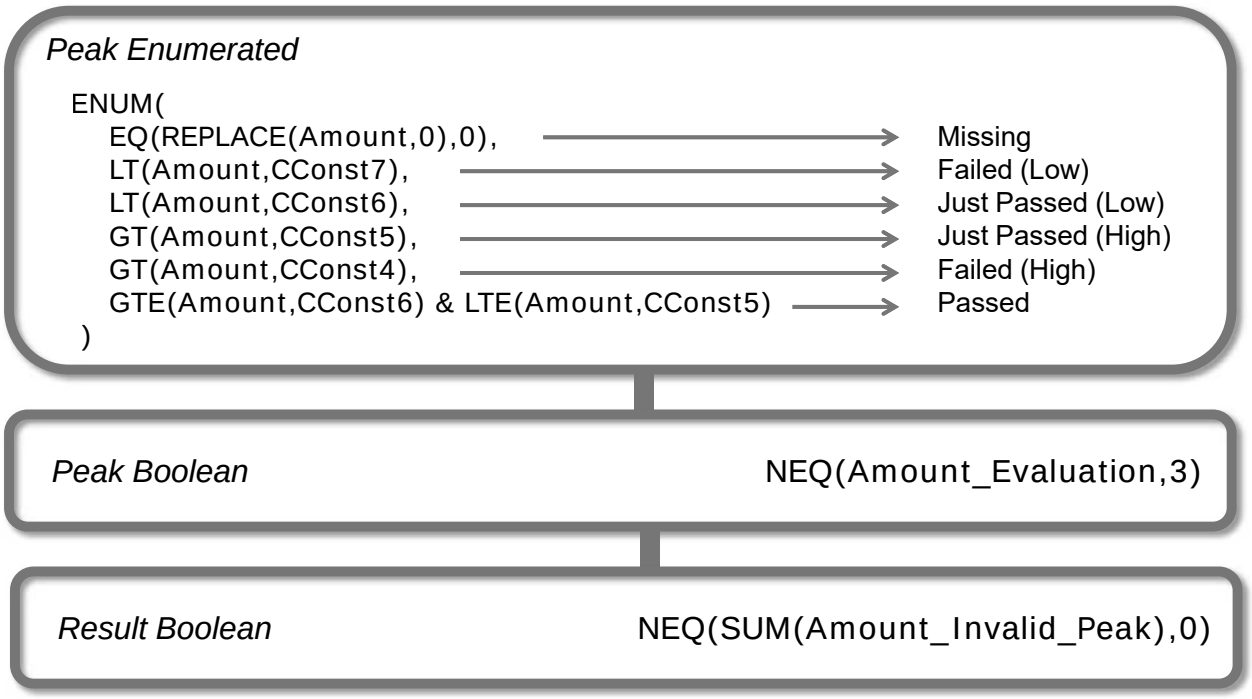


	SampleName	Result Id	Instrument Method Id	Instrument_Method_Valid
1	PQ Std. 2.5x	1247	1004	OK
2	PQ Unk. 1	1250	1004	OK
3	PQ Unk. 3	1252	1004	OK
4	PQ Unk. 4	1253	1004	OK

	SampleName	Result Id	Instrument Method Id	Instrument_Method_Valid
1	PQ Std. 2.5x	1247	1004	OK
2	PQ Unk. 1	1250	1031	Incorrect Instrument Method Used
3	PQ Unk. 3	1252	1004	OK
4	PQ Unk. 4	1253	1004	OK

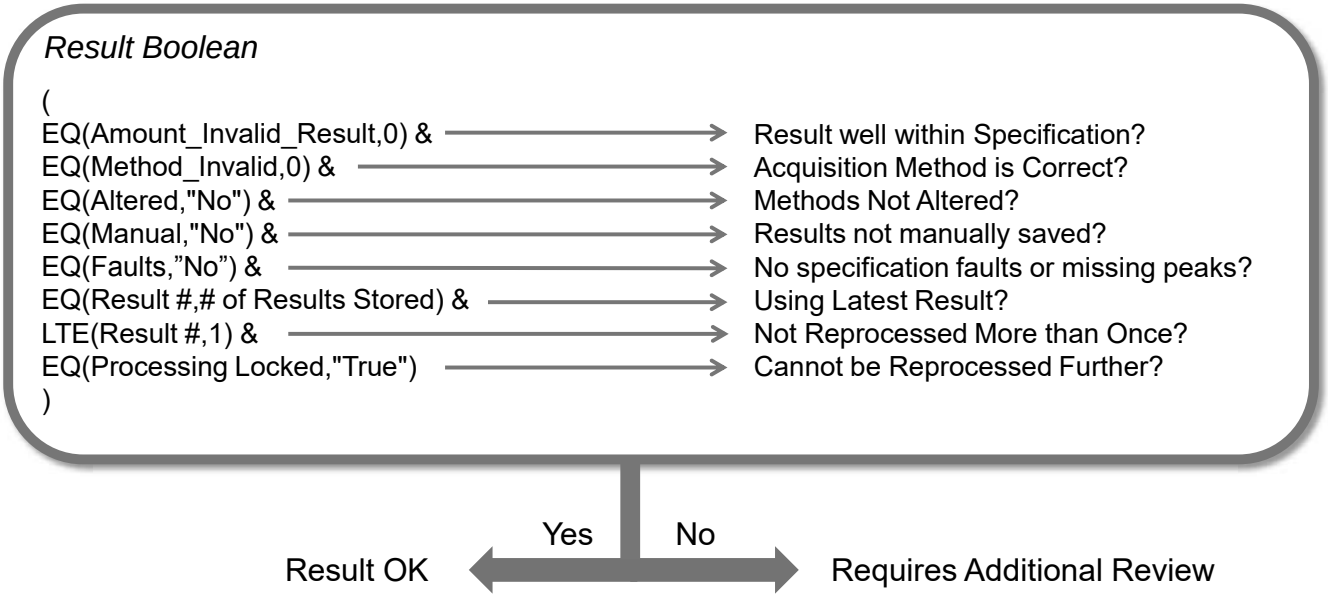
How Can We Review…

- Does the result ‘just pass’ the product specification?
  - Store the specification values in CConst 4, 5, 6 and 7



Minimising Manual Review

- To check everything that was in the previous ‘Partially Automated Review’ table…and specification limits checking…



Exception Review Evaluation

- Use calculations and logic in the application to determine ‘high-risk’ from ‘low-risk’ samples
  - Minimise manual interpretation
  - Build-in safety checks

	SampleName	Result Id	Result_Overview
1	PQ Std 10x	1039	OK
2	PQ Unk. 1	1040	OK
3	PQ Unk. 4	1043	OK
4	PQ Unk. 2	1041	OK
5	PQ Unk. 3	1042	OK
6	PQ Std. 2.5x	1037	OK
7	PQ Std 5.0x	1038	OK

Examples of Audit Trails – User’s Question

真相永遠只有一個！

Case 1

- Q: 為何其中一筆data只收了10分鐘?
- 從Run Samples畫面叫出的Sample Set Method, Run Time都是25分鐘呀?

File Edit View Inject Actions Customize Diagnostics Help

Run Only | Continue on Fault

Sample Set Method:

	Vial	Inj Vol (uL)	# of Injs	Label	SampleName	Level	Sample Matrix	Function	Method Set / Report Method	Label Reference	Processing	Run Time (Minutes)
1	10	5.0	1		Blank solution			Inject Samples			Normal	25.00
2	10	5.0	1		Blank solution			Inject Controls			Normal	25.00
3	11	5.0	1		Standard solution-			Inject Standards			Normal	25.00
4	12	5.0	1		Standard solution-			Inject Standards			Normal	25.00
5	13	5.0	1		Standard solution-			Inject Standards			Normal	25.00
6	14	5.0	1		Standard solution-			Inject Standards			Normal	25.00
7	15	5.0	1		Standard solution-			Inject Standards			Normal	25.00
8	16	5.0	1		Check Standard solution			Inject Standards			Normal	25.00
9	17	5.0	1					Inject Samples			Normal	25.00
10	18	5.0	1					Inject Samples			Normal	25.00
11	19	5.0	1		Standard solution-			Inject Standards			Normal	25.00

Case 1

- 從Sample Set Method的audit trail, 有兩個版本的記錄
- 從新版本的時間點, 發現新版本的時間是在實驗完成後…
- 比較兩個版本的"Differences", 發現從Run Time從10改為25

Sample Sets | Injections | Channels | **Methods** | Result Sets | Results | Peaks | Fractions | Sign Offs | C

	Method Name	Method Type	Method Date
1		Instrument	2018/4/23 PM 07:00:12 CST
2		Instrument	2018/4/23 PM 06:58:08 CST
3		Processing	2018/4/25 AM 09:13:31 CST
4		Processing	2018/5/28 PM 01:18:45 CST
5		Processing	2018/5/31 PM 04:05:06 CST
6		Processing	2018/4/26 PM 02:02:15 CST
7		Report	2018/4/26 PM 02:16:18 CST
8		Report	2018/4/23 PM 06:58:09 CST
9		Method Set	2018/4/23 PM 07:47:10 CST
10		Method Set	2018/4/23 PM 06:58:08 CST
11		Sample Set	2018/4/
12		Sample Set	2018/4/
13		Sample Set	2018/4/
14		Sample Set	2018/4/

Open... Ctrl+O
New Method
Method Properties...
Preview/Publisher
Print...
Run Samples
Copy To Project...
View As

Method Properties

Method Information
Name:
Type: Sample Set
Last Modified By:
Lock | Locked By:
Clear | Being Edited By:

Method History

	Method Name	Method Type	Method Comments	Method Date
1		Sample Set		2018/4/23 CST
2		Sample Set		2018/4/23 CST

Differences | Print Methods | Print History | Save As Current | Audit Trail

Case 2

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- Q: 為何"Result ID"沒有連號?

Peak Results

	SampleName	Result Id	Injection	Date Acquired	Sample Set Id	Processing Method	Processing Method Id
1	Bl k	1283	1	2018/5/22 PM 02:16:10 CST	1225	Impuruty	1272
2	Bl k	1284	2	2018/5/22 PM 02:52:32 CST	1225	Impuruty	1272
3	reference Standard	1285	1	2018/5/22 PM 03:28:51 CST	1225	Impuruty	1272
4	reference Standard	1286	2	2018/5/22 PM 04:05:26 CST	1225	Impuruty	1272
5	reference Standard	1287	3	2018/5/22 PM 04:41:46 CST	1225	Impuruty	1272
6	29-1	1288	1	2018/5/22 PM 05:18:19 CST	1225	Impuruty	1272
7	29-1	1289	2	2018/5/22 PM 05:54:39 CST	1225	Impuruty	1272
8	29-2	1290	1	2018/5/22 PM 06:31:02 CST	1225	Impuruty	1272
9	29-2	1291	2	2018/5/22 PM 07:07:21 CST	1225	Impuruty	1272
10	reference Standard	1273	1	2018/5/22 PM 07:43:45 CST	1225	Impuruty	1272

Case 2

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- "Result ID" – 沒有連號, 且1273號碼在其他Results之前
- "Manual" – "Yes" = 手動數據處理
- "Date Processed" – Result ID 1273 processing的時間在前, 且沒有和其他data一起做processing

Peak Results

	SampleName	Result Id	Injection	Date Acquired	Sample Set Id	Processing Method	Processing Method Id	Altered	Manual	Faults	# of Results Stored	Result #
1	Bl k	1283	1	2018/5/22 PM 02:16:10 CST	1225	Impuruty	1272	No	No	No	1	1
2	Bl k	1284	2	2018/5/22 PM 02:52:32 CST	1225	Impuruty	1272	No	No	No	1	1
3	reference Standard	1285	1	2018/5/22 PM 03:28:51 CST	1225	Impuruty	1272	No	No	No	1	1
4	reference Standard	1286	2	2018/5/22 PM 04:05:26 CST	1225	Impuruty	1272	No	No	No	1	1
5	reference Standard	1287	3	2018/5/22 PM 04:41:46 CST	1225	Impuruty	1272	No	No	No	1	1
6	29-1	1288	1	2018/5/22 PM 05:18:19 CST	1225	Impuruty	1272	No	No	No	1	1
7	29-1	1289	2	2018/5/22 PM 05:54:39 CST	1225	Impuruty	1272	No	No	No	1	1
8	29-2	1290	1	2018/5/22 PM 06:31:02 CST	1225	Impuruty	1272	No	No	No	1	1
9	29-2	1291	2	2018/5/22 PM 07:07:21 CST	1225	Impuruty	1272	No	No	No	1	1
10	reference Standard	1273	1	2018/5/22 PM 07:43:45 CST	1225	Impuruty	1272	No	Yes	No	1	1

Case 3

- Q: 為何第一次、第二次用的Processing Method都相同，扣Blank之後的Data會不一樣?

第一次 process

Peak Results

	Name	RT	Area	Int Type	Conform
1			5949419	Group	

Peak Results

	Name	RT	Area	Height (μV)	Int Type
1		12.195	137846	973	BV
2		15.216	32860	2191	W
3		17.448	130819	1435	W
4		19.355	37538	1825	W
5		20.777	59710	1504	W
6		21.300	296078	8229	W
7		23.065	5949419	207366	W
8		26.601	131202	2923	VB
Sum			6775472.2		

第二次 process

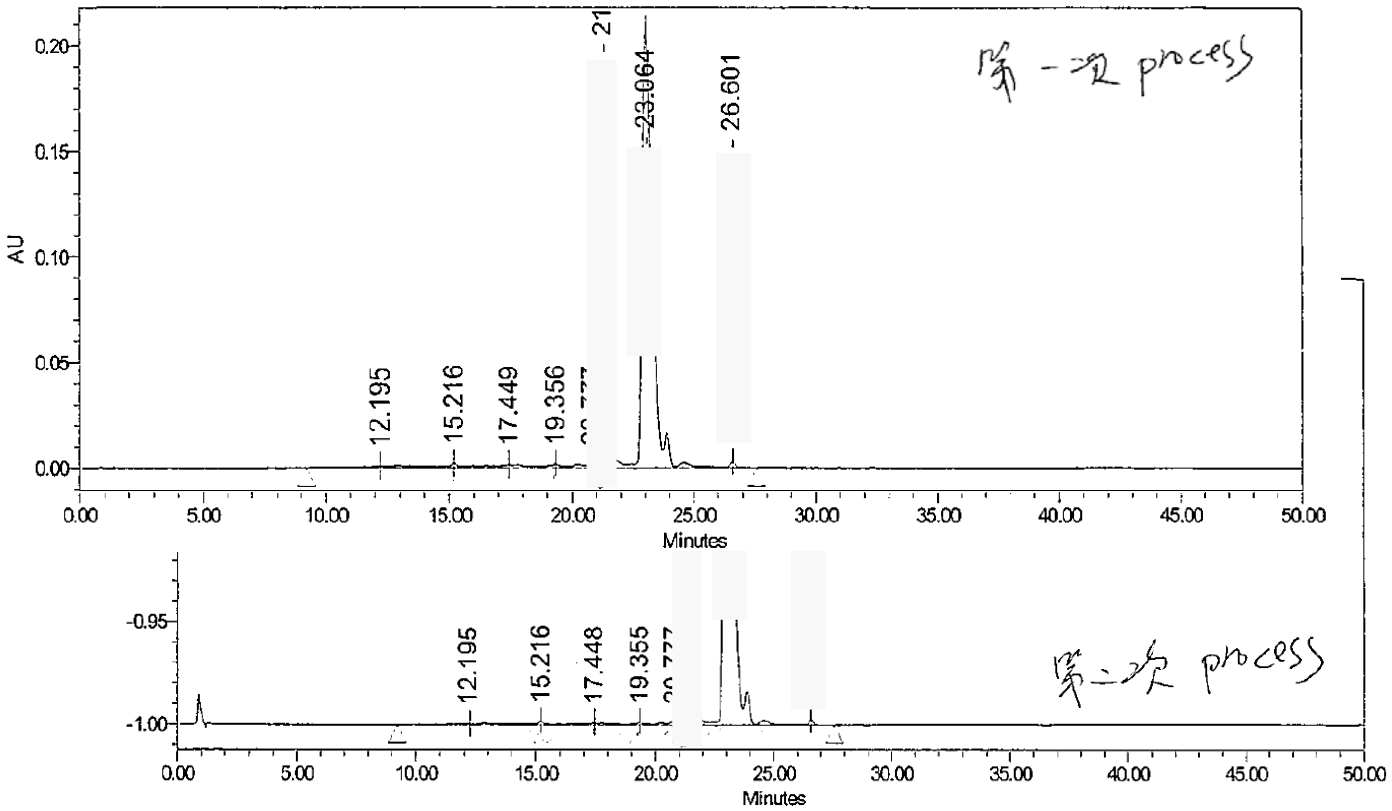
ak Results

Area	Int Type	Conform
5964245	Group	

Peak Results

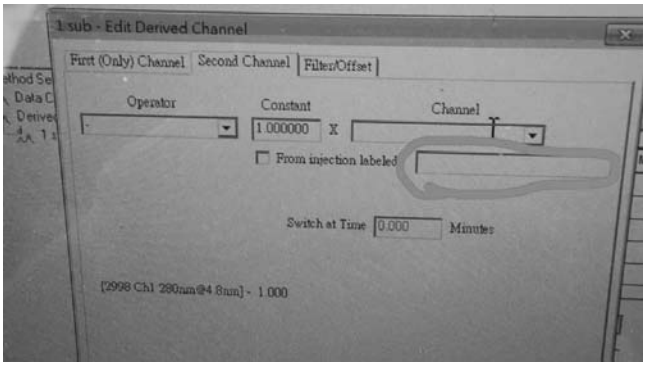
Name	RT	Area	Height (μV)	Int Type
	12.195	172106	1076	BV
	15.216	38009	2373	W
	17.449	174572	1653	W
	19.356	46733	2041	W
	20.777	70140	1691	W
	21.300	310958	8426	W
	23.064	5964245	207527	W
	26.601	141380	2948	VB
		6918142.5		

Case 3



Case 3

- 第二次process的那筆data沒有扣到Blank, 整張圖譜扣了1 AU, 必須確認用來處理數據的Method Set有沒有問題

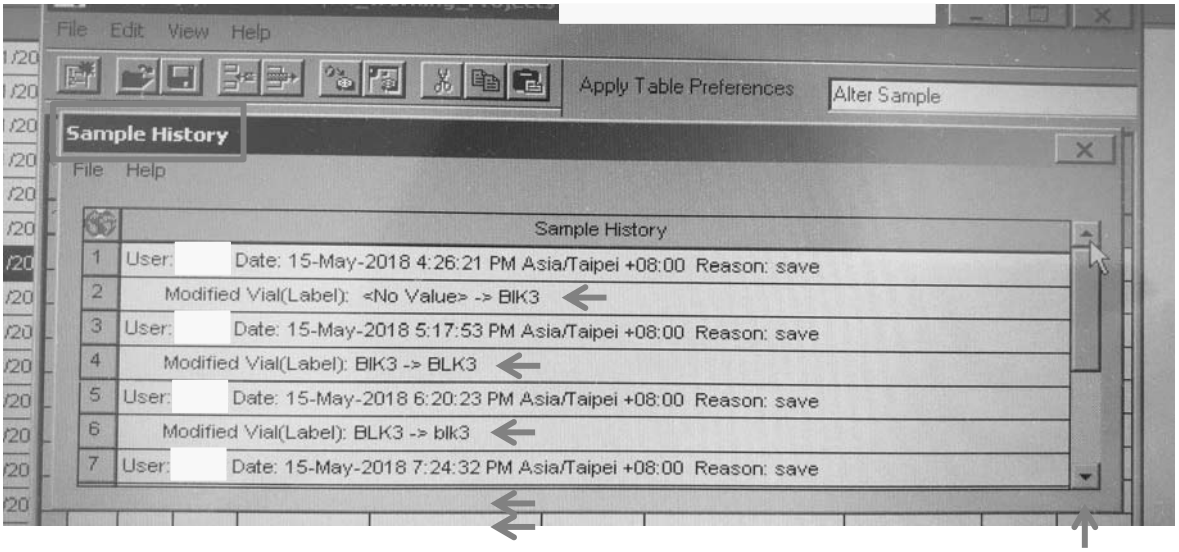


- Q: 兩筆data所選用的Method Set是同一個, 而且Method Set最後設定完成的儲存時間是在5/15 PM 4:30, 兩次積分皆在此時間之後
  - ✓ check第一次process時間: 15-May-2018 5:38:14 PM
  - ✓ check第二次process時間: 16-May-2018 9:47:03 AM
  - ✓ 也調閱了Method Audit Trail, 無異常記錄

- 只剩一個可能…

Case 3

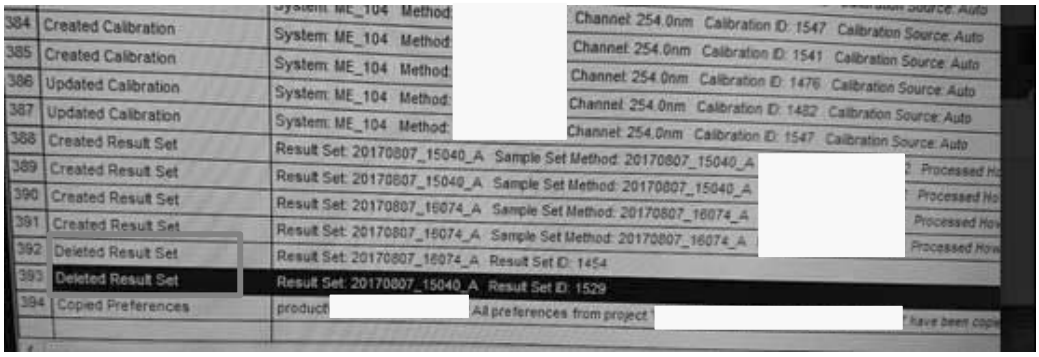
- Blank沒有被正確Label, 要看一下Sample Audit Trail, view sample history
  (第一次process時間: 15-May-2018 5:38:14 PM)
  (第二次process時間: 16-May-2018 9:47:03 AM)

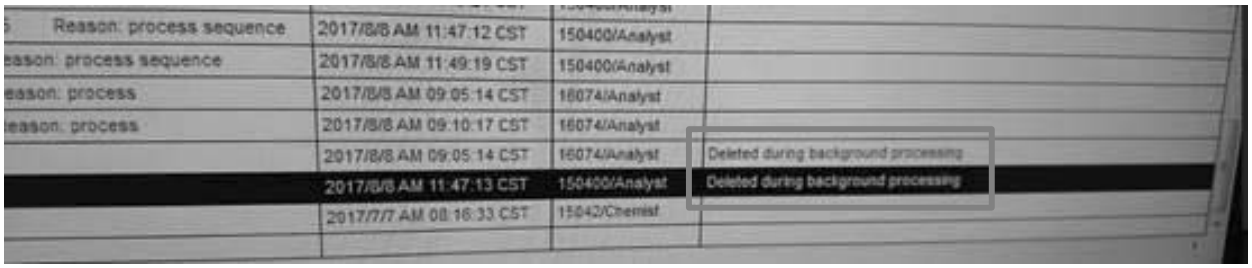


Case 4

- Q: Audit Trail “Action” – **Deleted** Result Set ???

  Audit Trail “Misc” – **Deleted** during background processing ???





Case 4

- This Result Set was not deleted by user, Empower deleted it during background.

- The reason that no results were generated was that the project tablespace was exhausted. But other things might also cause not results to be create:
  - ✓ Processing attempted with a Method Set that is missing either a derived channel, or a Processing Method.
  - ✓ Processing attempted with a Processing Method that does not match the channels (e.g. and MS processing method with a fluorescence channel)

Case 4

- http://www.waters.com/waters/support.htm?lid=43575&type=USCT

iRequest Technical Service / Support
Support
Support Library
How To Videos
Safety Data Sheets
Spare Parts
Instrument Upgrades
Instrument Services and Support
System Implementation
Software Services and Support
Professional Services

ResultSet Deleted during background processing

Primary Product:	Empower
Content Type:	Usability/Consistency
Category/Screen:	Audit Trail Generation
Platform:	ALL
Operating System:	Not Applicable
PCS Number:	43575
Product Version:	Empower
Software Option:	All
Version Corrected:	Not a Defect
Related Products:	Empower

Abstract / Summary

When background processing fails to create results, Empower automatically deletes the empty result set and posts the "No results produced for this processing job" message to the Message Center. In the audit trail, the deletion is attributed to the user who submitted the processing job, even if that user does not have Delete privileges.

To determine how a result set was deleted, check the audit trail. When Empower deletes a result set, the audit trail Misc field contains the text "Deleted during background processing". When a user deletes a result set, the user's comments appear in the Details field after "Reason:", and the Misc field is blank.

See PCS 45715

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