Empower® 3

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Empower 3 Electronic Data Review

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Microsep

Waters Division

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Empower Traceability

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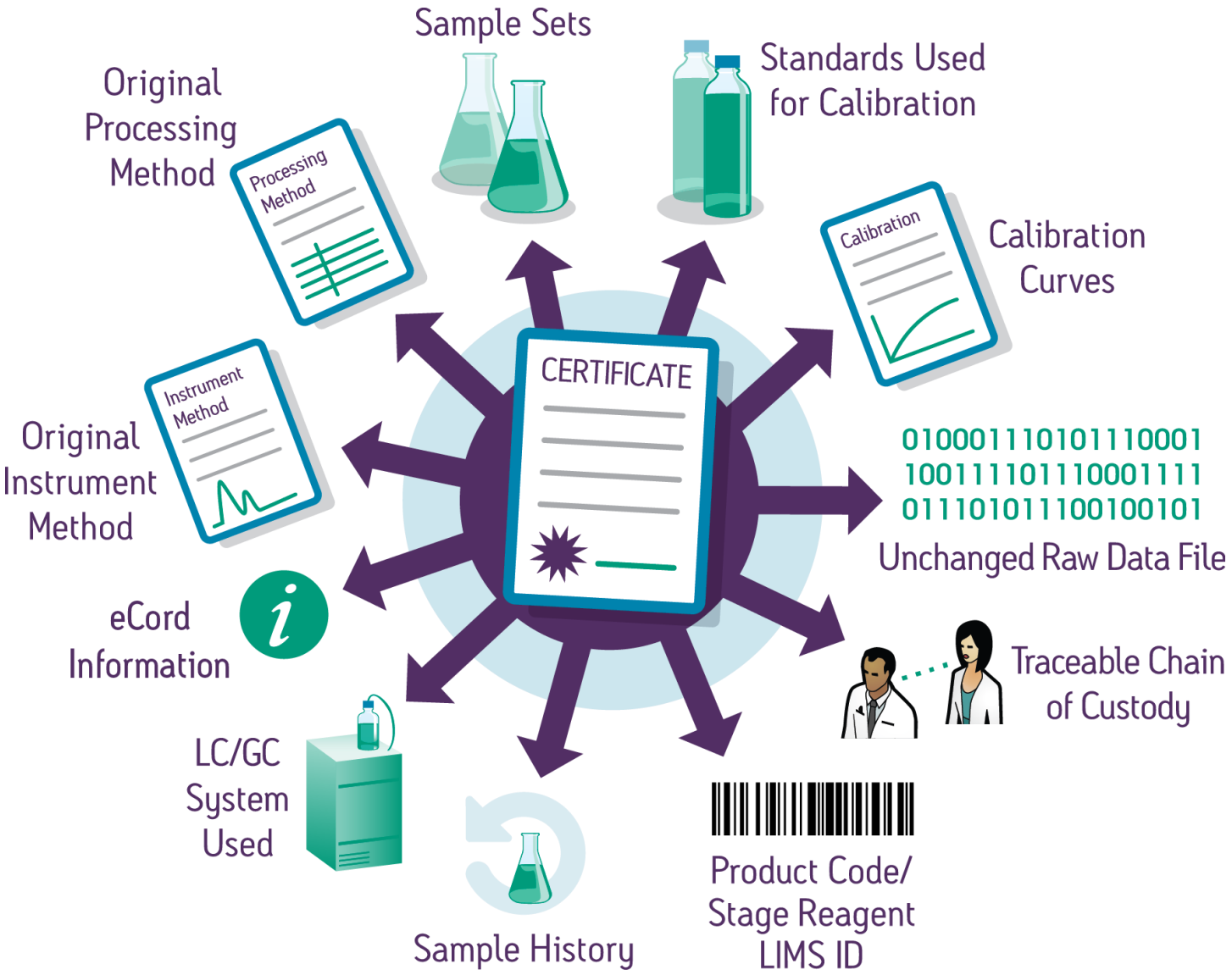

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Ensuring Adherence to Rules

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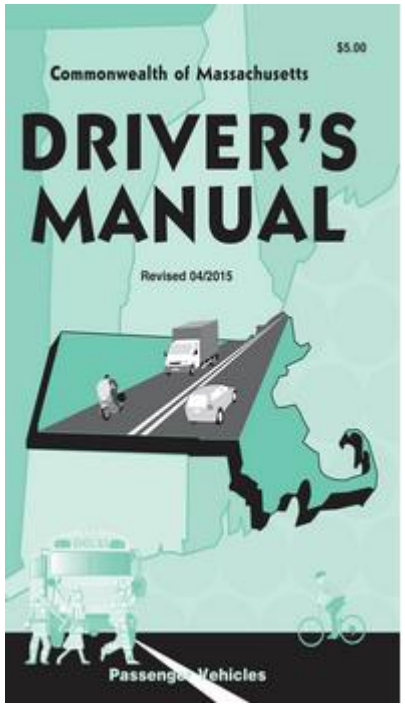

Never drive faster than the **posted speed limit**. Sample speed limit signs appear on the next page. All speed limits are based on ideal driving conditions. If conditions are hazardous, you must drive slower.

- What makes me drive slower/safer?
- Technical Controls
- Intense “Highway Review” procedure

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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.**
- **Justification should be documented**
- **Should be retained**
- **Available for review**

GxP Data Integrity Definitions and Guidance for Industry
DRAFT July 2016

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Key Topics of Part 11 and Annex 11

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- Secure Records
  - Back up, archive, records retention policy of ALL data and meta data
  - Easy retrieval of e-records and Human Readable copies
  - ontrolled access with unique username and password
  - Secure computer generated audit trails for any changes to data
- Applications that work
  - Validation
  - Training
- Electronic Signatures
  - Non repudiation of signature (if using)

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FDA Draft Data Integrity Guidance:
System Suitability & Test Runs

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

- Not consistent with CGMP
- Disguising testing into compliance.
- If an actual sample is to be used for system suitability testing,
  - properly characterized secondary standard,
  - written procedures
  - the sample should be from a different batch
  - All data should be included in the record

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

FDA U.S. FOOD & DRUG ADMINISTRATION

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

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Is it acceptable to only save the final results from reprocessed laboratory chromatography?

- No
  - *If chromatography is reprocessed, written procedures must be established and followed*
    - ***All results 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

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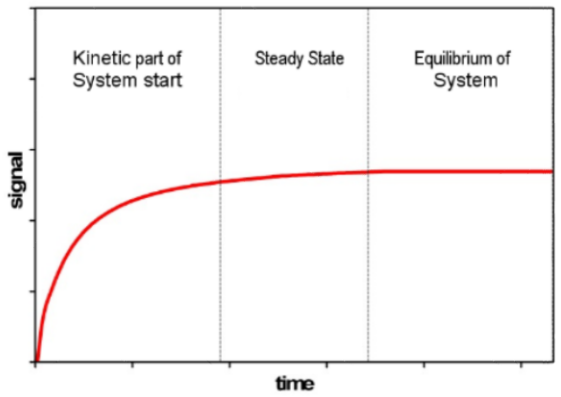
Acquiring Samples SOP



- **Test Injections:** System Readiness checks
  - Define 'WHAT' they are:
    - Never Samples
    - Possibly a standard
    - An independent solution which mimics real samples
  - Define 'HOW' they will be used:
    - Never delete them
    - How is it assessed visual check, calculations performed, reported or not
    - How do you proceed when it doesn't meet the criteria
  - Define 'WHEN' they will be performed:
    - Every run, when runs are not successive
    - As part of the sample set, as individual injections
- **System Suitability:** As part of the Sample Set/Result Set
  - If System Suitability fails… or "just" passes define the next steps
    - should you continue the run, repeat from the beginning with justification

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Processing Results SOP Suggestions

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- **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

- **Policies:**
  - **Hide "amount" fields in Review while adapting integration parameters**
  - **Prevent Calibration/Quantitation in Review**
  - **Prevent saving results from Review**

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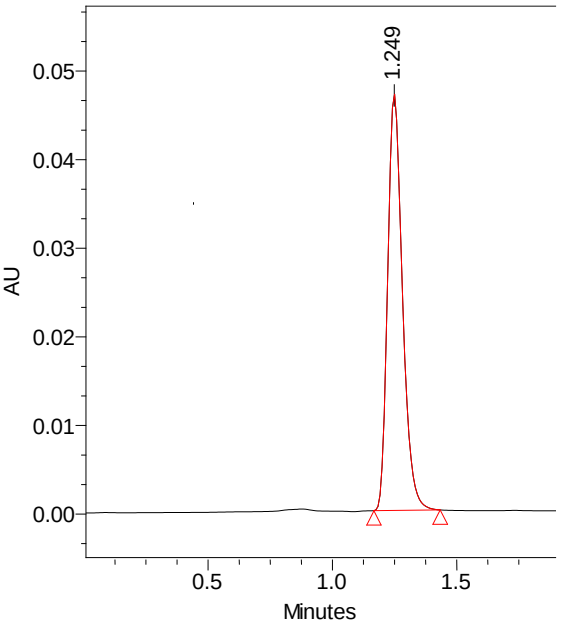
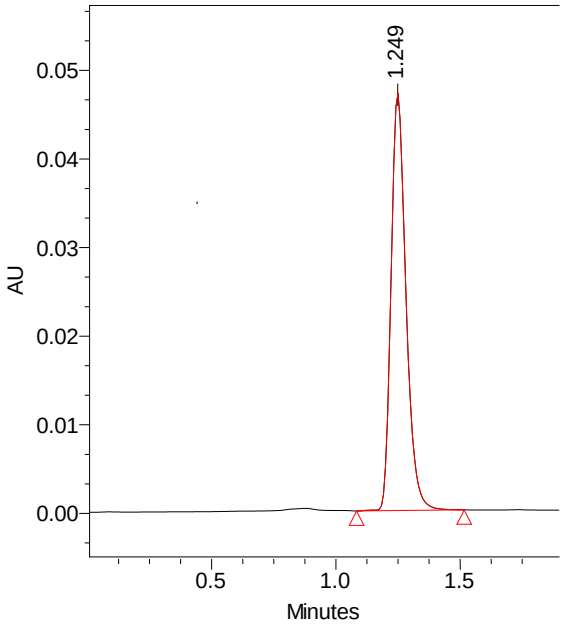
The history of integration is important



Version 1
Fail Criteria



Version 2
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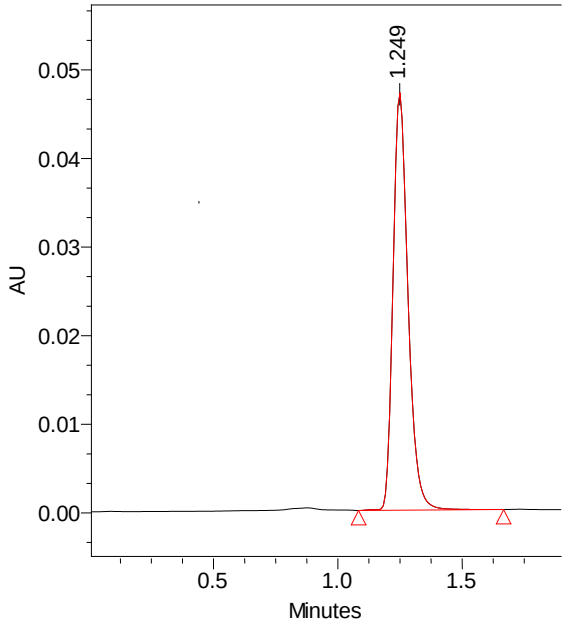

Version 3
Pass Criteria

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

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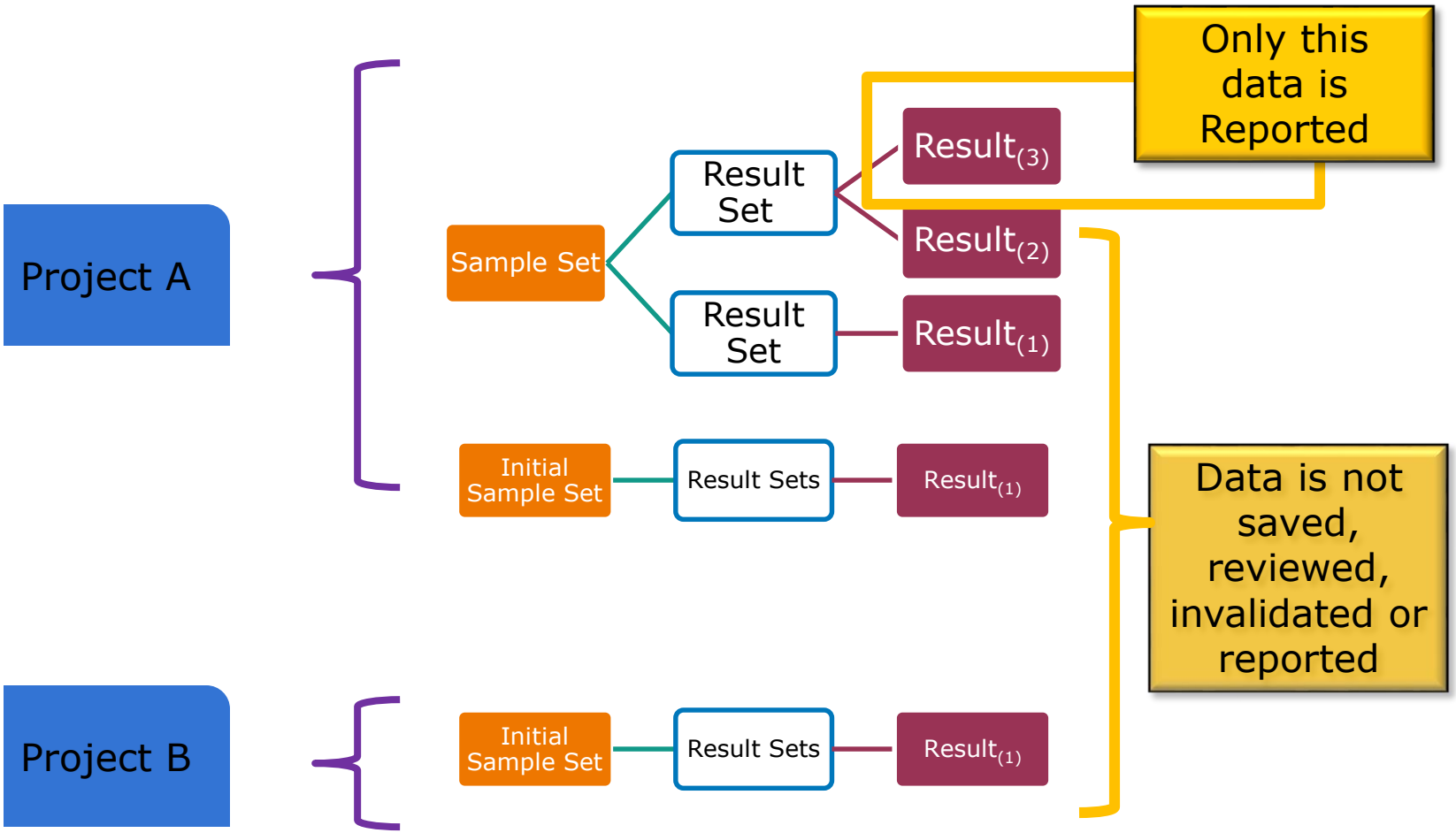

- Technical controls (project access and project creation) are important, other technical controls may not exist

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Orphan Data

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- Data not included in final reports
- Documented scientific reasons for its invalidation
- 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

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How do I know what to review?

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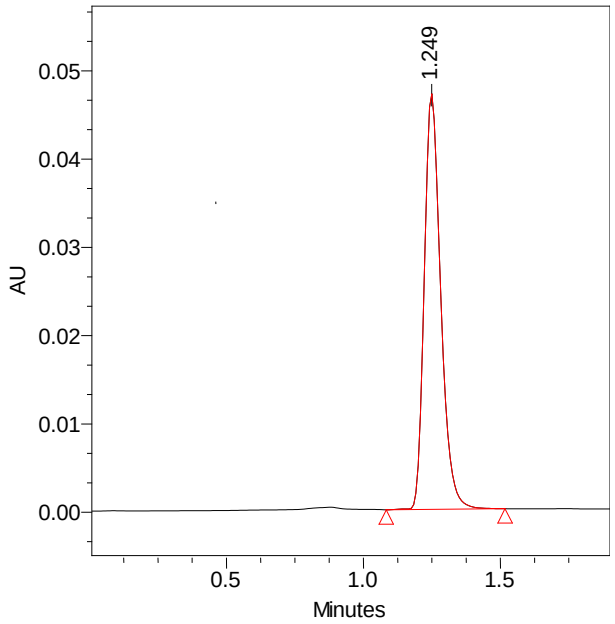
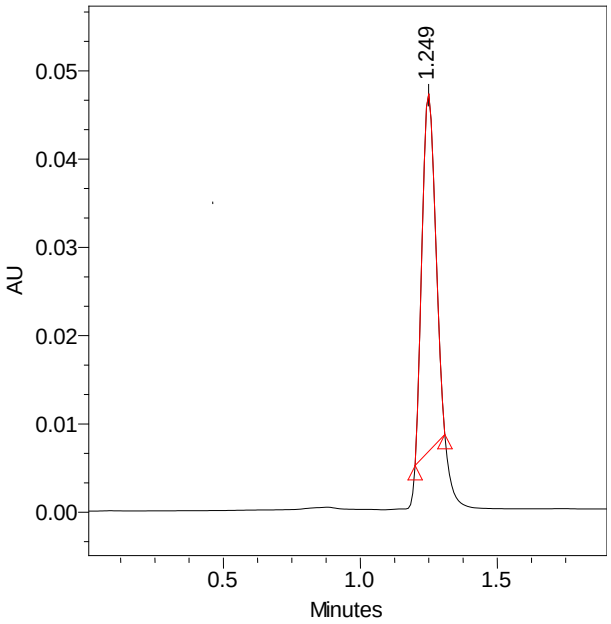


Version 1: Fail Criteria



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

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What IS the right integration?

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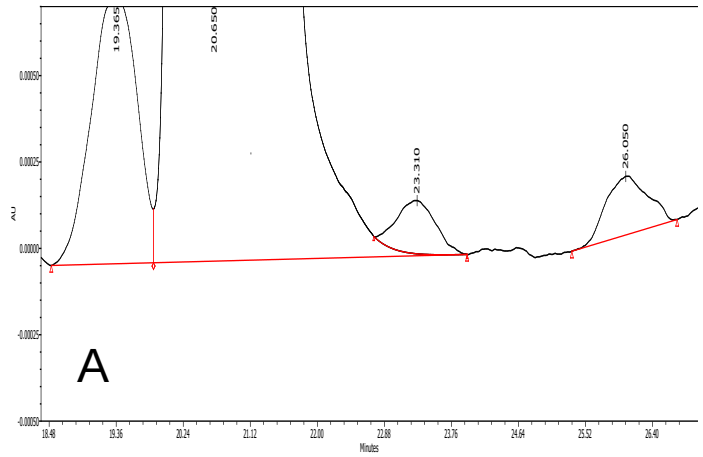

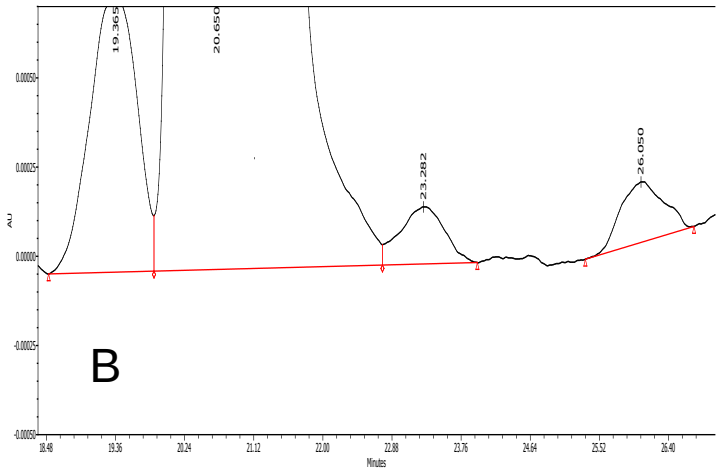

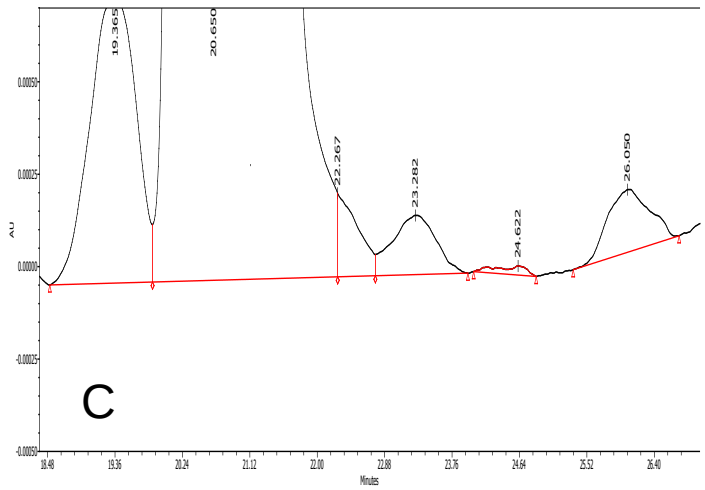

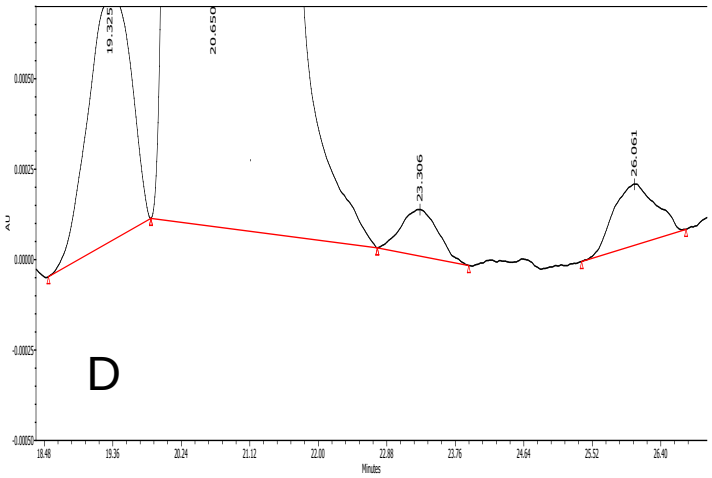

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Avoid discussion on ‘right integration’

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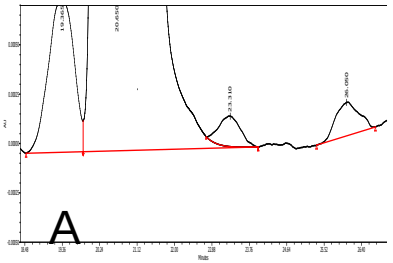
- Optimize method resolution to have baseline resolution: **UPLC**
- Save and review all versions of results based on risk
- Training on correct use of Integration parameters
  - Uses **Apex Track** to improve “first time right”
  - Don’t specify “parameters” specify “outcome” : (Like PAT)
  - Include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



- Allow Manual Integration where required…..
- “Automatic” processing hides complex and manipulative integration methods
  - No visibility to Reviewers
  - Extremely time consuming
  - May include Manual integration by “Method”
    - Eg force peak……

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Which integration is most accurate?

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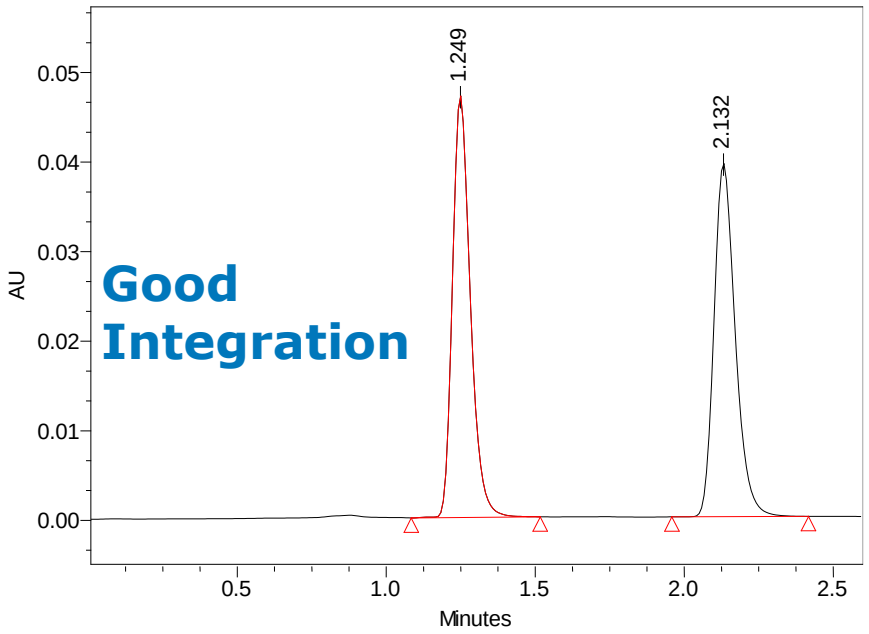
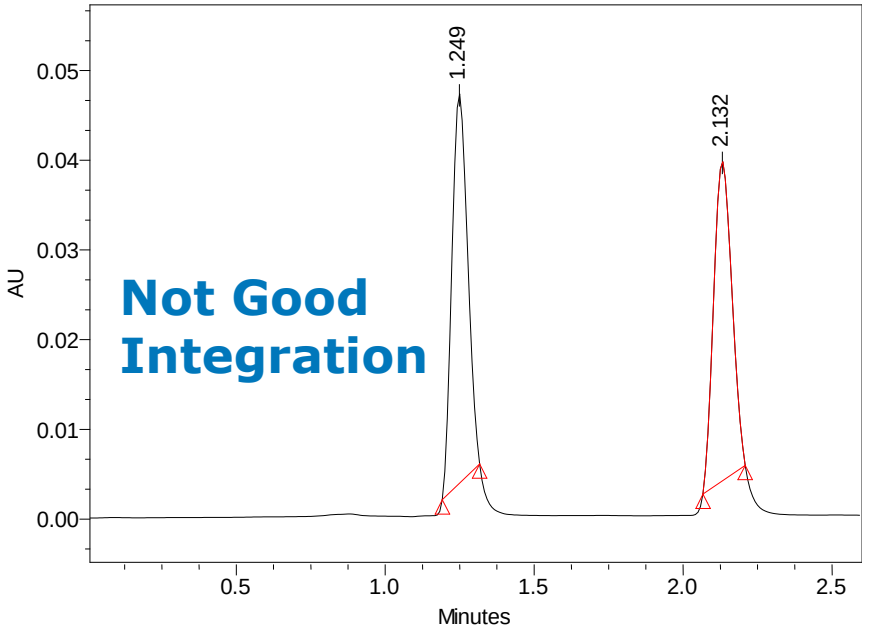
Pass



Fail



Manual

Processing Method

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

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Annex 11 Audit Trails

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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.

- Audit trails tell us WHO did WHAT, WHEN automatically
- Audit trails tell us WHY as defined by the user
- They have two primary purposes:
  - Give a history to the data, to help decide if it can be trusted
  - They should deter wrongdoing (think of CCTV)
    - Without review, they are not a deterrent

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What would you look for in System Audit Trail?

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- Deleting data only by designated administrators and WHY
- Creating projects only by designated administrators
- Regular archiving of projects / altering access or status of projects
- Altering System Policies
- User creation patterns
- Password resetting activity
- Unauthorised access to system
- Alteration of systems
- Changes to roles
- Access to system at non working time
- Restore of Projects and Project Integrity
- Check on performance of IQ (Warning, Error)
- Archive and Removal of Audit Trail
- Unsuccesful Attempt to Confirm Identity

In the Empower Help: Actions recorded in system audit trails

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WHO Guidance:
Audit Trail Review Summary

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- …may include discrete event logs, history files, database queries or reports
- Regular review of audit trails may reveal incorrect processing of data and help prevent incorrect results from being reported and identify the need for additional training of personnel;
- All GxP records held by the GxP organization are subject to inspection by health authorities. This includes original electronic data and metadata, such as audit trails.
- Risk based…frequency roles, responsibility and approach
  - .. **periodic review** of audit trails that track system maintenance activities,
  - …audit trails that track changes to critical GxP data..would be expected to be reviewed **each and every time the associated data set is being reviewed and approved** – and prior to decision-making.
- Data review should be documented.
  - For electronic records, this is **typically signified by electronically signing the electronic data set that has been reviewed and approved.**

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

World Health Organization

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Review of Audit Trails

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- **Review audit trails as part of data review process**
  - Find anomalies before batch release
  - Focus of user behaviour that affect results
  - Peer Review / Manager review / QA review?
- **Periodic Review of overall/system level audit trails**
  - system level activity without correct documentation, change control, testing or approval
    - eg. changing system policies, user access or deletion of data
- **Inspectors WILL look at the audit trails in electronic data systems**

Biggest Issue: Audit trails are often more a log of all activity (to comply) and not designed for easy review

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Review of Audit Trails

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Print Audit Trails

- Include data relevant audit trails in regular reports
- Periodically print out System level audit trails to "review"
- Sign reports as "evidence" of review

Review Audit Trails Electronically

- Use the tools (if any) built into the CDS
- Review as PART of the data/integration /method review
- Write a clear SOP defining which audit trails to review and when
  - Only flagged or suspicious results?
- Signing results includes declaration of electronic review

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Empower Audit Trail summary

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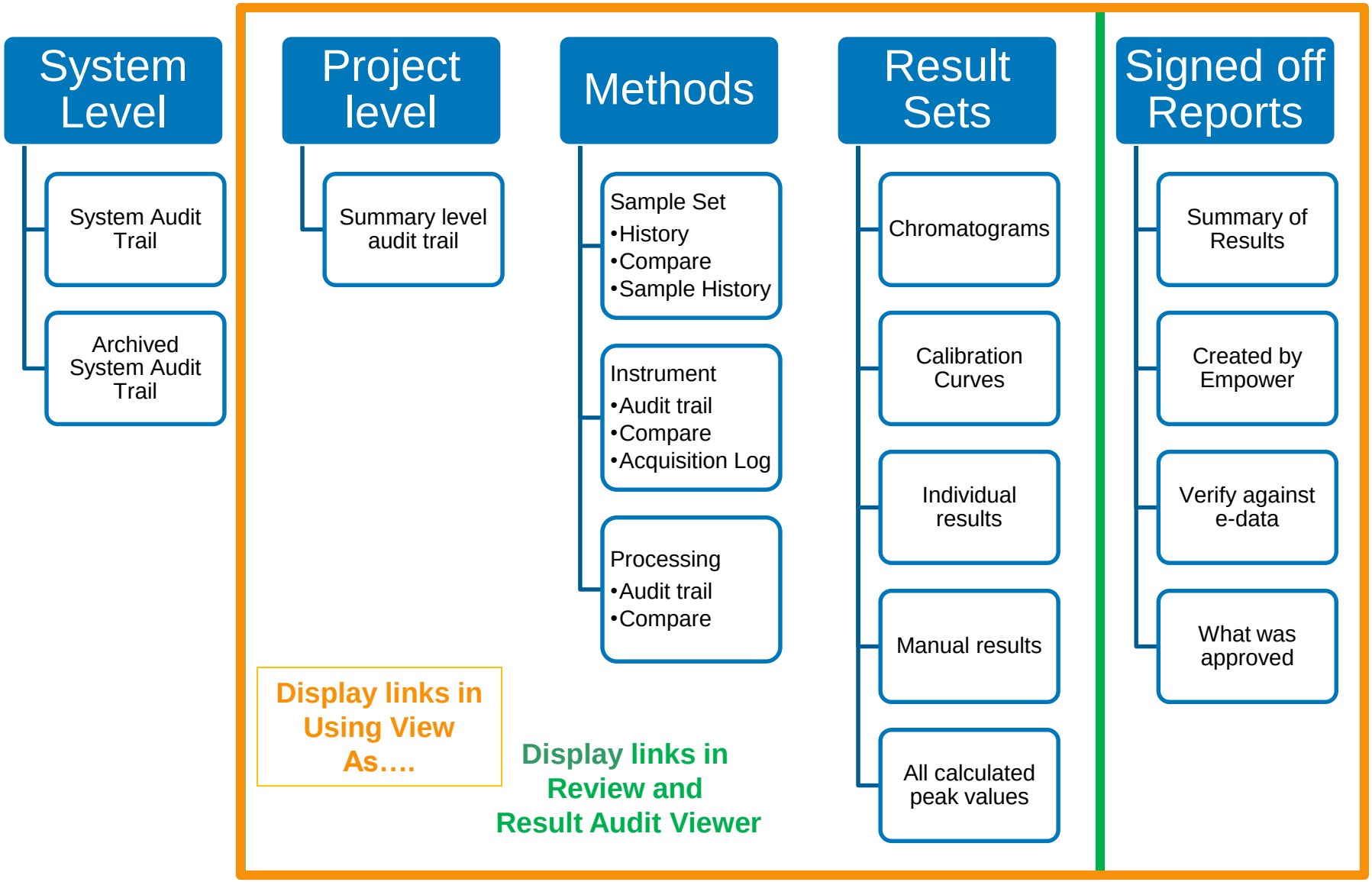

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Empower Audit Trails

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- Project Audit Trail
  - Gives overview of all changes in a project
  - Includes details of method / data deletion
  - View as Audit Records…
- System Audit Trail
  - shows changes to system objects and system policies
  - details archive activity
  - notes all changes to security (users, user types etc)
  - documents all successful and unsuccessful logins
    - you have a history of who was logged into the application at any time
    - you have information about system break in attempts
    - includes the client the login/login attempt occurred at
- Offline System Audit Trail
  - for viewing historical System Audit Trails which have been archived

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Empower Audit Trails

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- Sample and Sample Set Audit Trail
  - Tracks changes to entered data about each sample
- Acquisition and Injection Logs
- Result Audit Trail
  - Links results to instruments, sample sets, methods, calibration curves and standards used in calibration.
  - Also traces any manual manipulation of data
- Method Audit Trail
  - Instrument, SampleSet, SampleSet Method Templates, Processing, Report, Export
  - Keeps all versions of method for recreation of results
  - Audit Trail monitors each change, before and after values, who when and why
  - Different versions can be compared to identify the differences

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The Review Tool

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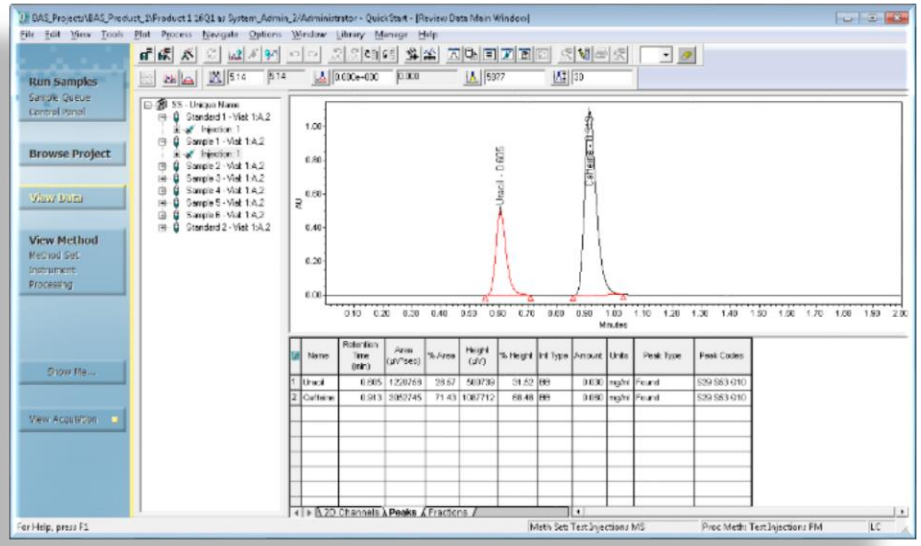
- Access to integrated chromatograms /results
  - All integration positions
  - Ability to zoom in to examine without reprocessing
- Peak and Result level values
- Used Instrument Method
- Used Processing Method
- Calibration Curves
- Added Direct access Sample Set and Sample Set History
- Added access to audit trails with Result Audit Viewer
- Direct connection to Preview for Sign Off capabilities



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Result Audit Viewer Tool

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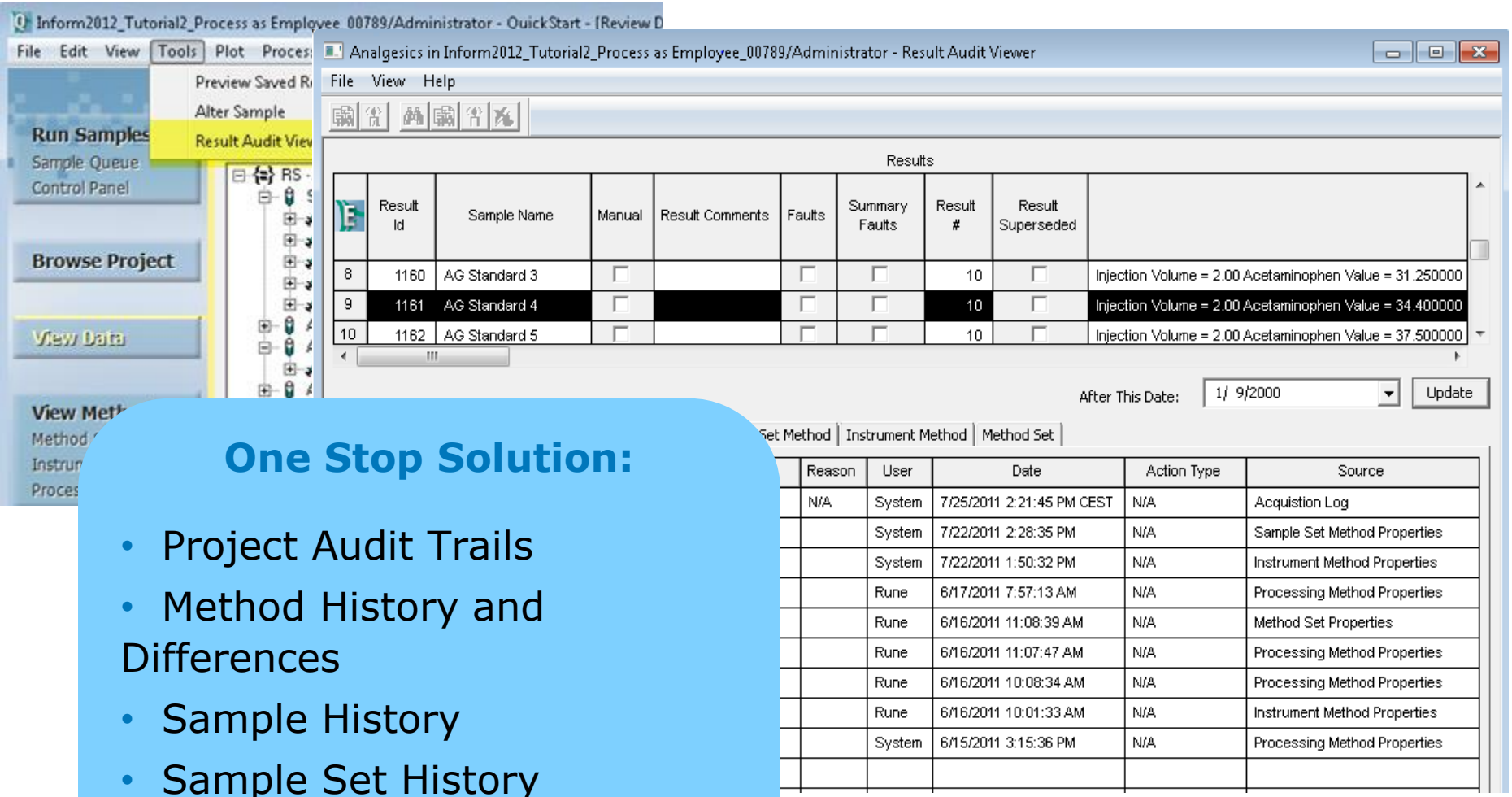

One Stop Solution:

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

New in Feature Release 2

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Acquisition Log

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Result History | Result Differences | Processing Method | Sample Set Method | Instrument Method | Method Set

	Details
1	Details: System: Alliance with 2487 Method: Test Channel: 2487Channel 1 Calibration ID: 1034 Calibration Source: Auto
2	Details: Result Set: Sample Set 1 Sample Set Method: SS 1 Method: Test Processed How: Processing Method Result Set ID: 1033 Sample Set ID: 1022
3	Details: Method: Test Type: Processing Version: 1
4	Version 1 9/21/2016 11:10:28 AM EDT User System
5	Acquired By : System Injection : 1 Date Acquired : 9/21/2016 11:01:37 AM EDT Run Time : 3.50 Acq Method Set : test Injection Volume : 5.00 Barcode / BCD : Auto Additions : Injection Id : 1024
6	User changed flows to: 1.10 (%A 40.0 %B 60.0 %C 0.0 %D 0.0) and limits to: Low 0.00, High 4000.00 at 0.95 minutes
7	User changed flows to: 1.10 (%A 40.0 %B 60.0 %C 0.0 %D 0.0) and limits to: Low 0.00, High 4000.00 at 0.95 minutes

Date	Action Type	Source
9/21/2016 11:17:30 AM EDT	Created Calibration	Audit Trail Record
9/21/2016 11:17:30 AM EDT	Created Result Set	Audit Trail Record
9/21/2016 11:10:28 AM EDT	Created Method	Audit Trail Record
9/21/2016 11:10:28 AM	N/A	Processing Method Properties
9/21/2016 11:01:37 AM EDT	N/A	Acquistion Log
9/21/2016 11:01:37 AM EDT	N/A	Injection Log
9/21/2016 11:01:37 AM EDT	N/A	Injection Log

Acquisition Log

Acquired By	System
Injection	1
Date Acquired	9/21/2016 11:01:37 AM EDT
Run Time	3.50(Minutes)
Acq Method Set	test
Injection Volume	5.00(uL)
Barcode / BCD	
Auto Additions	
Injection Id	1024
Instrument Method Id	1018
Instrument Method Name	test
Superseded	No
# of Process Only Sample Sets	0
eCord Name	
eCord Serial Number	
eCord Injection Count (Lifetime to Date)	
eCord Sample Count (Lifetime to Date)	
eCord Maximum Pressure (Lifetime to Date)	(psi)
eCord Maximum Temperature (Lifetime to Date)	(°C)
Use Syringe Settings	
Syringe Size A (uL)	
Nanoliter Adapter A	
Syringe Size B (uL)	
Nanoliter Adapter B	

User changed flows to: 1.10 (%A 40.0 %B 60.0 %C 0.0 %D 0.0) and limits to: Low 0.00, High 4000.00 at 0.95 minutes
User changed flows to: 1.10 (%A 40.0 %B 60.0 %C 0.0 %D 0.0) and limits to: Low 0.00, High 4000.00 at 0.95 minutes

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Adding audit trails to reports

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Sample History

User: System Date: 8/15/2011 7:17:54 PM IST Reason: save
Modified Vial(SampleName): Gemfibrozil Sample -> Assay Sample
User: System Date: 7/17/2014 6:03:25 PM IST Reason: for demo
Modified Vial(Batch_Number): <No Value> -> 1
Modified Vial(Batch_Number1): <No Value> -> 1
Modified Vial(Column_ID): <No Value> -> 1
Modified Vial(Column_ID1): <No Value> -> QC/LC/001
Modified Vial(Molecular_Wt1): <No Value> -> 1.000
Modified Vial(Molecular_Wt2): <No Value> -> 1.000
Modified Vial(SampleWeight): 1.0000 -> 50.0000

Review Sample Information **Result Set Id 1138**

	Sample Name	Result ID	Sample Set ID	Instrument Method ID	Processing Method ID	Altered	Result #	# of Results Stored	# of Sign Offs	Processing Locked	Manual	Result Codes
1	Standard 1	1145	1057	1004	1023	No	3	3	0	True	No	S02
2	Sample 1	1147	1057	1004	1023	No	3	3	0	True	No	S02
3	Sample 2	1148	1057	1004	1023	No	3	3	0	True	No	S02
4	Sample 3	1149	1057	1004	1023	Yes	3	3	0	True	No	S02
5	Sample 4	1150	1057	1004	1023	No	3	3	0	True	No	S02
6	Sample 5	1153	1057	1004	1121	Yes	4	4	0	False	Yes	S02
7	Sample 6	1151	1057	1004	1023	No	3	3	0	True	No	S02
8	Standard 2	1146	1057	1004	1023	No	3	3	0	True	No	S02

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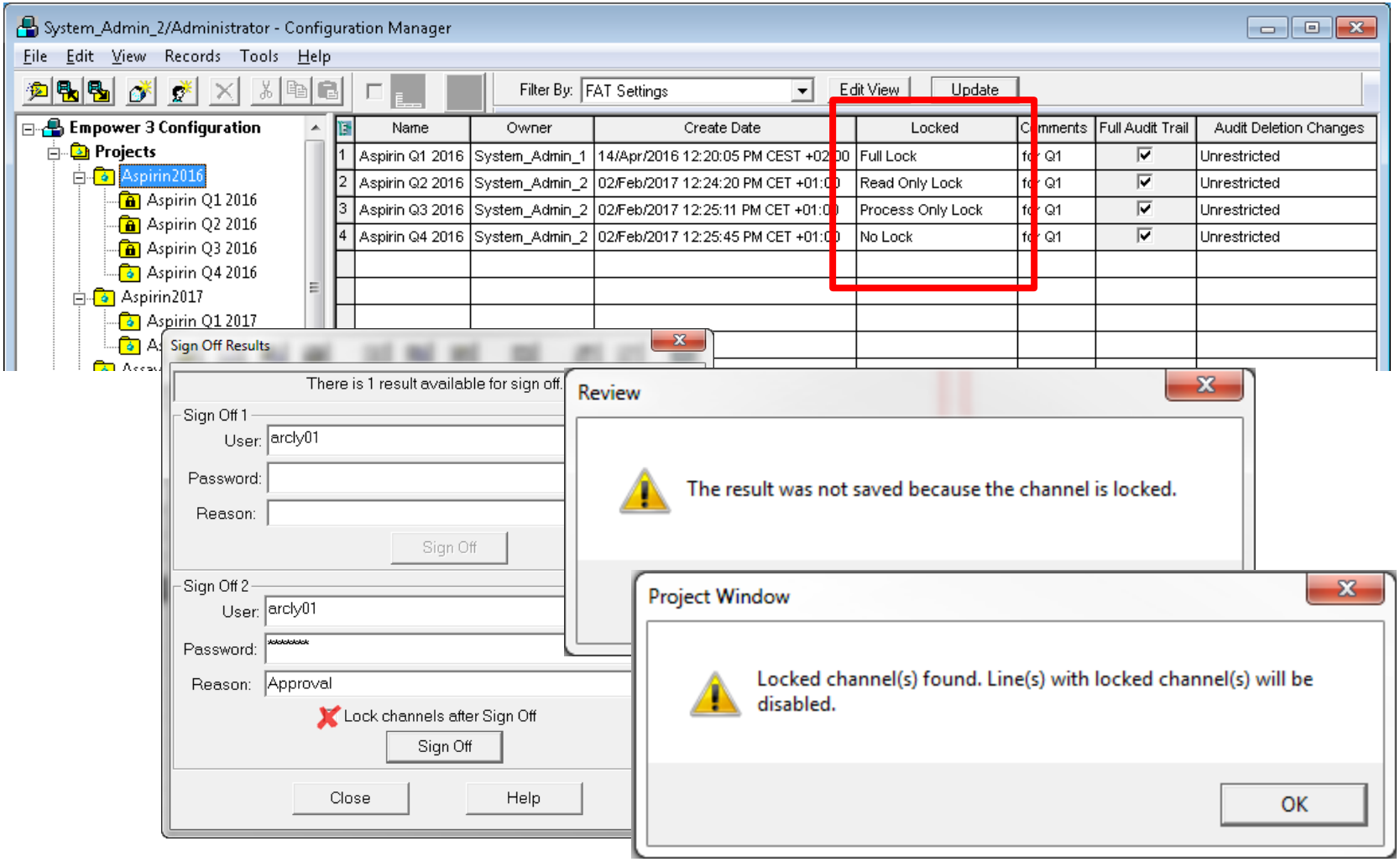
Lock Projects and Channels



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

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How to document Data Review including Audit Trails

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- Review chromatograms, methods and relevant Audit Trails in Empower application
- Document that process by SIGNATURE : see the WHO Guidance
  - 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

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Data Review SOP suggestions

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- 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
- 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

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Periodic Review

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- It's like an internal audit on the compliance of the system
  - Find concerns BEFORE the audit
  - Find ways to improve the efficiency of systems and processes
  - **Documented evidence of actively searching for data integrity issues**
  - Eg Review System Audit Trail for correct use of Admin functionalities
- Review major and minor changes to determine if any retesting or additional testing of new functionality is required
  - Has it significantly expanded or changed use
  - **Is the system still in control and in a validated state?**
- How often?
  - Frequency may depend of maturity and criticality (3-18monthly)
- **A formal report must be written about the review**
  - **Its a regulatory requirement**

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