Solution towards a vendor-neutral and secure transfer of data between LIMS and Instruments

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on behalf on an interdisciplinary working group originating from the e-environment community

The Challenge

Improve data security and data integrity in LIMS-to-Instrument integration.

Typical bioanalytical integration scenario:

- Transferring sequence **worklist information** from a LIMS to an LC-MS instrument

- Returning LC-MS **result information** back to a LIMS

… to form a secure and compliant closed loop

The journey to improved data security and DI compliance

The challenge reported in EBF White Paper

'Current products still force the bioanalytical laboratories into manual and time-consuming quality-control steps to mitigate the DI risks. With the increased number of citing's during health authority inspections over the last few years, the message is clear: DI issues must be resolved!'

The objective cited in EBF White Paper

Our focus on LC/MS–LIMS interface has many immediate benefits: **primarily reducing the time and effort required to manually perform quality control of data transfer**. The proposal should also be seen as a move away from the current status quo and to showcase that progress can be made relatively simple if and when all agree on a common standard.

White Paper

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Improving data integrity in regulated bioanalysis: proposal for a generic data transfer process for LC–MS from the European Bioanalysis Forum

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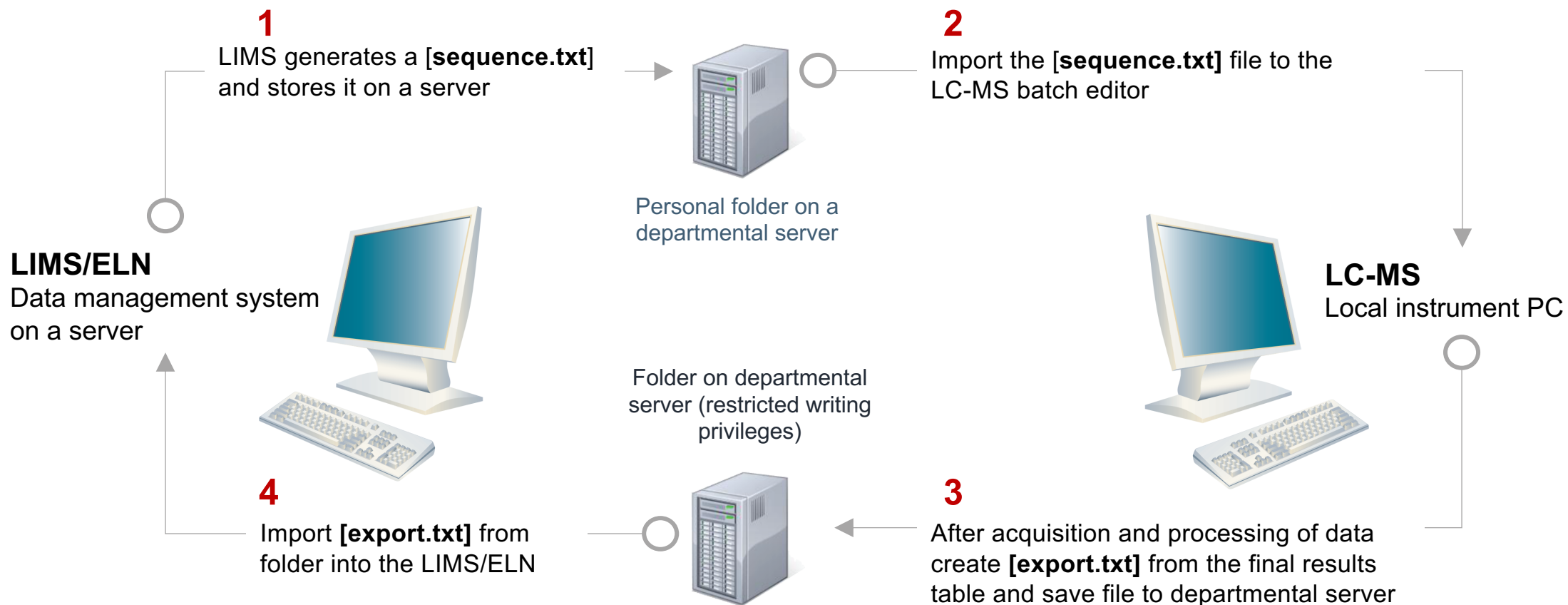*Author for correspondence: chair@e-b-f.eu

This resulted in a **joint effort of the user and vendor community** to create a vendor-neutral, standards-based solution, as reported in this presentation.

A traditional data transfer cycle

Current data transfer cycles require manual and time-consuming quality-control steps to mitigate the DI risks. Limitations include; ASCII / human readable files, it is a proprietary solution, and it is not secure.

1
LIMS generates a [**sequence.txt**] and stores it on a server

2
Import the [**sequence.txt**] file to the LC-MS batch editor

Personal folder on a departmental server

LIMS/ELN
Data management system on a server

LC-MS
Local instrument PC

Folder on departmental server (restricted writing privileges)

4
Import [**export.txt**] from folder into the LIMS/ELN

3
After acquisition and processing of data create [**export.txt**] from the final results table and save file to departmental server

Key points for a solution

Transferring sequence information from a LIMS to a LC-MS instrument and exporting LC-MS results back to a LIMS.

Mitigate DI risks
Making make data transfer more secure
Make it easier to audit

Have a near-zero impact for any user experience
The proposed changes for any LC-MS user are near-zero.
Sample batches can be loaded from the same folder location and results exported with a single click
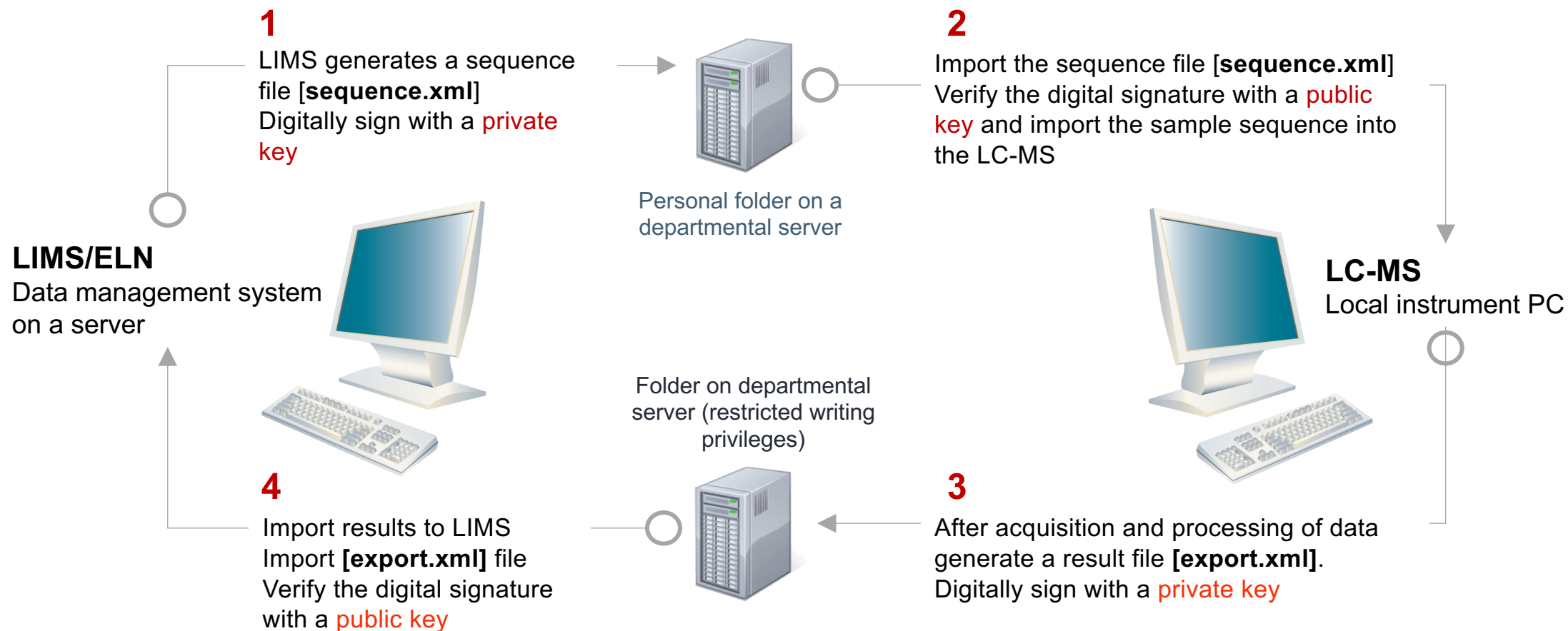
Standardized solution for all software / instrument interfaces
No proprietary solution required for specific LIMS-Instrument combinations

A proposed way forward; replacing .txt files with digitally signed .xml files

Advantages include; Ascii / human readable files, it is a standardized solution, and it is a secure
The security is based upon a private-public key digital signature pairing

1
LIMS generates a sequence file [**sequence.xml**]
Digitally sign with a private key

Personal folder on a departmental server

2
Import the sequence file [**sequence.xml**]
Verify the digital signature with a public key and import the sample sequence into the LC-MS

LIMS/ELN
Data management system on a server

LC-MS
Local instrument PC

Folder on departmental server (restricted writing privileges)

4
Import results to LIMS
Import [**export.xml**] file
Verify the digital signature with a public key

3
After acquisition and processing of data generate a result file [**export.xml**].
Digitally sign with a private key

Solution towards a vendor-neutral and secure transfer of data between LIMS and Instruments

The technical solution

The key point is to mitigate DI risks by making make data transfer more secure, but it is also important to make it easier to audit and have a near zero impact for any user experience

Standardized Format

Worklist/result information is transferred as a **vendor neutral XML file format** (data model is flexible and scales beyond LC-MS workflows; open to all instrument providers; reuses existing schemas).

- Data model is derived from the AnIML format
- Flexible and scalable beyond LC-MS domain

Standardized Security

Improving security by signing the files with a digital signature using Public / Private key – logic, provided by the World Wide Web Consortium (W3C) Signature Working Group.

- Attributable – you can tell who made a signature
- Tamper-evident – you can tell if data has changed since signing
- Automated validation – before accepting a file, instrument or LIMS can confirm its provenance
- Stored in XML – easy to read and write, broad developer experience
- Royalty free logic – free libraries for Java, .net, …

The proposed model has 2 files; a worklist file and a results file

The core content was identified in the EBF White Paper
However, it is important to note that the AnIML file format is scalable, and more fields could be added

LIMS to LC-MS Worklist File

Run/File specific fields
Study/project
Run/batch file
User good laboratory practices (GLP)
Plate barcode
File name

Sample specific fields
Sample name/ID
Sample barcode/ID
Analyte(s)/internal standard(s) name
Dilution factor
Order number
Plate position
Sample type
Concentration

LC-MS to LIMS Results File

Run/File specific fields
Study
Run
Date/time
User
Plate barcode
File name
User comments

Sample specific fields
Sample barcode/ID
Analyte(s)/internal standard(s) name
Analyte raw data (peak area, peak height, ratio, etc.)
Analyte(s) concentrations data
Dilution factor
Plate position

Fields which have been identified in the **EBF White Paper Bioanalysis (2020) 12(14), 1033–1038.**

Solution towards a vendor-neutral and secure transfer of data between LIMS and Instruments

What is a private/public key pairing and a digital signature?

This slide highlights the sequence file data transfer from the LIMS to LCMS (the same technology is used for the return trip back from the LCMS back to the LIMS)

LIMS
Sequence file

Digitally sign a file
LIMS private key

aZhxHC51QF
rBKCUeAwJk
3wn+/

LIMS
Private key – to lock files

LCMS
File can now be opened by the LCMS software

Verify the signed file
LIMS public key

LIMS
Public key – to verify files
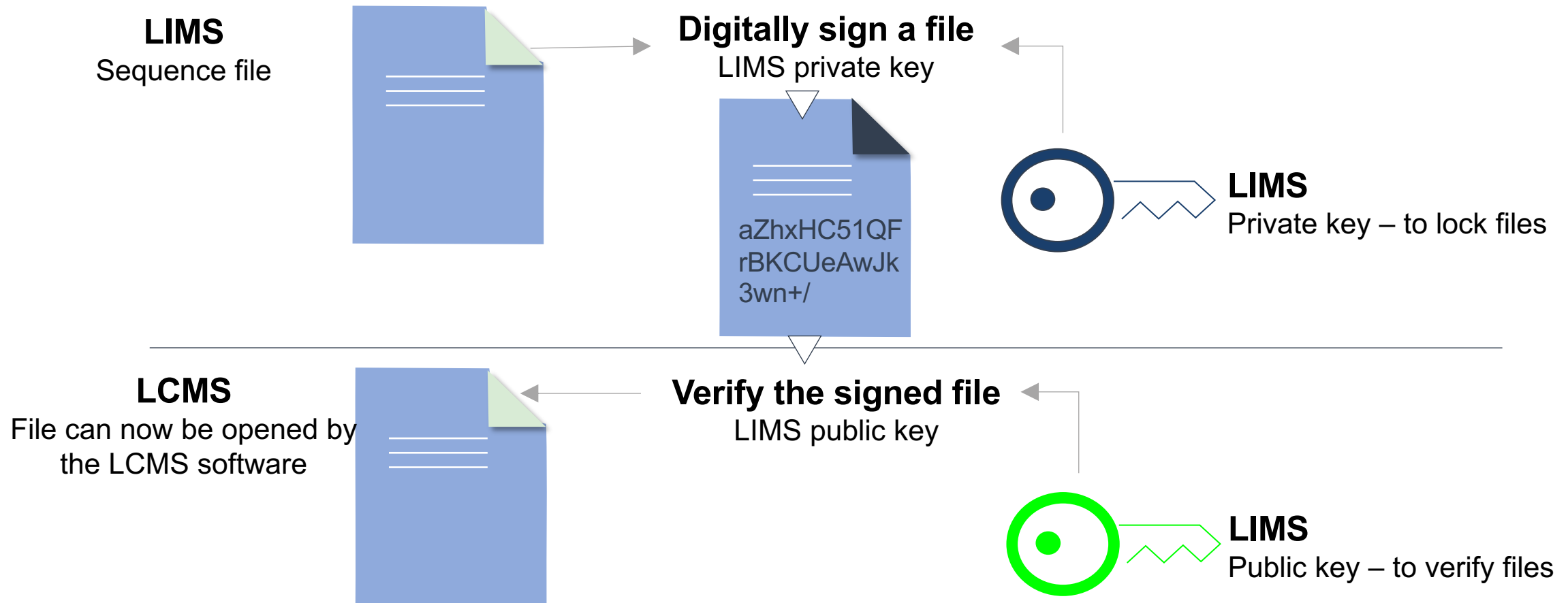
No change in 'user experience'

A user will be able to open a worklist file, review data and export results, as 'usual'.

1

LIMS | Generates a sequence file

2

LC-MS | The LC-MS user opens the sample batch list from a folder and acquires LC-MS data

3

LC-MS | Results are reviewed, checked and exported to the LIMS

4

LIMS | Stores the data

Under the hood

LIMS | generates a sequence file, converts it into a digitally signed XML file format with a public key and sent to the 'watcher' folder.

LC-MS | opens the sequence file and verifies the signature with a public key to make sure it has not been tampered with. A batch file is created to run samples

LC-MS | the results are sent to an export file, the results are converted into an XML format and digitally signed with a private key. The file is sent to the LIMS watcher folder.

LIMS | opens the digitally signed export.xml file with a public key and verifies it has not been tampered-with. Results are then stored into the LIMS.

Solution towards a vendor-neutral and secure transfer of data between LIMS and Instruments

Step 1: Export sequence from the LIMS/ELN

Generating a digitally signed [**sequence.xml**] file
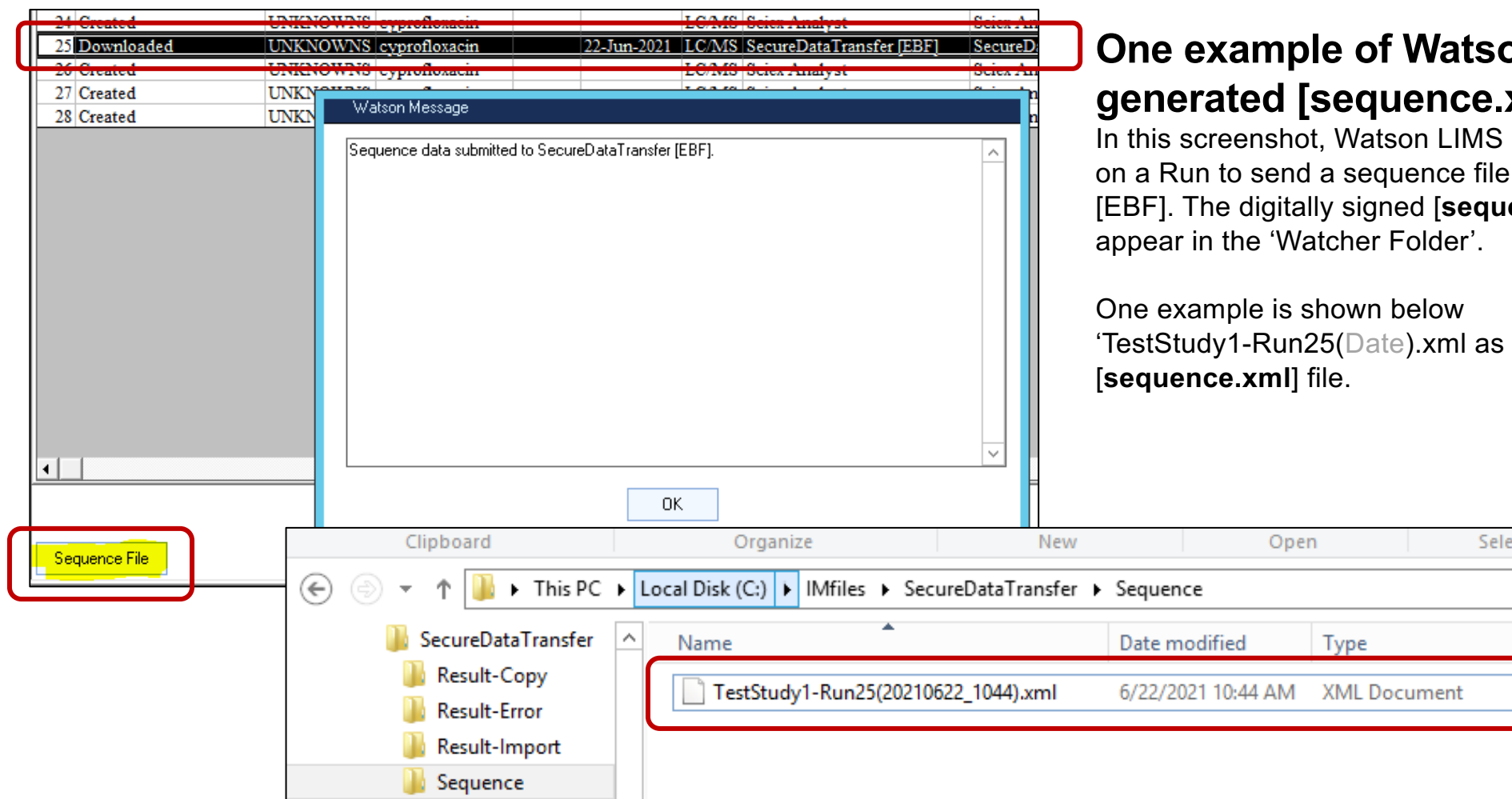
One example of Watson LIMS™ generated [sequence.xml] file

In this screenshot, Watson LIMS users would simply click on a Run to send a sequence file for secure Data Transfer [EBF]. The digitally signed [**sequence.xml**] file would then appear in the 'Watcher Folder'.

One example is shown below 'TestStudy1-Run25(Date).xml as the digitally signed [**sequence.xml**] file.

Solution towards a vendor-neutral and secure transfer of data between LIMS and Instruments

Step 2: user opens a sample batch file and acquired LC-MS data

The digitally signed sequence.xml file has been verified by the LC-MS software and the content has been converted to a vendor specific sample batch file which can be opened as 'usual' from a specified location.

Zero change to the user experience

The LC-MS software detects the [**sequence.xml**], verifies the signature and converts the file into the LC-MS sample batch format. The LC-MS user opens the sample batch file in the LC-MS application software.

One example is shown below.
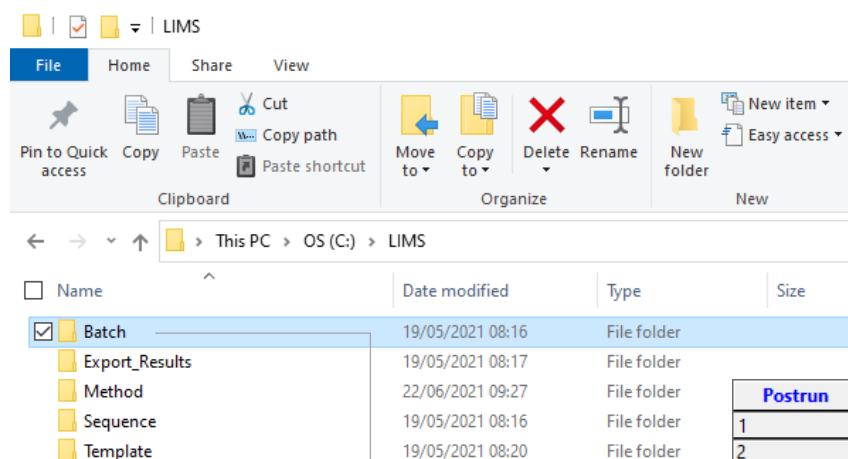
LC-MS user

Selects the sample batch file in the 'usual folder location' and opens the sample list in the LC-MS software

Postrun	Tray	Vial#	Sample Name	Sample ID	Sample Type	Method File	Data File	Data Comment
1	1	1	CalibnStd1	PlasmaCalibnStd_0.9695 pg/mL	1:Standard:(I)	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level1_ID1.lcd	Study_XH1179
2	1	2	CalibnStd2	PlasmaCalibnStd_1.939 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level2_ID2.lcd	Study_XH1179
3	1	3	CalibnStd3	PlasmaCalibnStd_3.879 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level3_ID3.lcd	Study_XH1179
4	1	4	CalibnStd4	PlasmaCalibnStd_7.08 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level4_ID4.lcd	Study_XH1179
5	1	5	CalibnStd5	PlasmaCalibnStd_20.14 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level5_ID5.lcd	Study_XH1179
6	1	6	CalibnStd6	PlasmaCalibnStd_40.28 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level6_ID6.lcd	Study_XH1179
7	1	7	CalibnStd7	PlasmaCalibnStd_105.922 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level7_ID7.lcd	Study_XH1179
8	1	8	CalibnStd8	PlasmaCalibnStd_210.352 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level8_ID8.lcd	Study_XH1179
9	1	9	CalibnStd9	PlasmaCalibnStd_280.469 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level9_ID9.lcd	Study_XH1179
10	1	10	CalibnStd10	PlasmaCalibnStd_350.586 pg/mL	1:Standard	LC-MSMS_BioanalysisMethod.lcm	CalibnStd_Level10_ID10.lcd	Study_XH1179
11	1	11	QC checks	AQC	2:Control	LC-MSMS_BioanalysisMethod.lcm	QC_LevelAQC_ID1.lcd	Study_XH1179
12	1	12	QC checks	LQC	2:Control	LC-MSMS_BioanalysisMethod.lcm	QC_LevelLQC_ID2.lcd	Study_XH1179
13	1	13	QC checks	MQC	2:Control	LC-MSMS_BioanalysisMethod.lcm	QC_LevelMQC_ID3.lcd	Study_XH1179
14	1	14	QC checks	HQC	2:Control	LC-MSMS_BioanalysisMethod.lcm	QC_LevelHQC_ID4.lcd	Study_XH1179
15	1	15	TimePoint_Pre-Do	AccessionCode_IDX1179_ZX1	0:Unknown	LC-MSMS_BioanalysisMethod.lcm	SampleID_t0_ID1.lcd	Study_XH1179
16	1	16	TimePoint_0.08h	AccessionCode_IDX1179_ZX2	0:Unknown	LC-MSMS_BioanalysisMethod.lcm	SampleID_t0.08_ID2.lcd	Study_XH1179
17	1	17	TimePoint_0.25h	AccessionCode_IDX1179_ZX3	0:Unknown	LC-MSMS_BioanalysisMethod.lcm	SampleID_t0.25_ID3.lcd	Study_XH1179
18	1	18	TimePoint_0.50h	AccessionCode_IDX1179_ZX4	0:Unknown	LC-MSMS_BioanalysisMethod.lcm	SampleID_t0.50_ID4.lcd	Study_XH1179

Step 3: Export Results (Shimadzu)

Review data and export results

Zero change to the user experience

LC-MS results are reviewed, if changes are made they can be documented in a standard audit trail. In this research application the results are exported to 'EBF LIMS' using a single click.

[Please note, the term EBF LIMS Integration is simply a 'placeholder name' in this research application build]

Export message (Shimadzu)
A simple confirmation

Exporting results to the LIMS
Once the export icon is clicked the results are then automatically processed by the LC-MS software;
- Results are converted into the **[export.xml]** format.
- The **[export.xml]** file is signed with a digital private key and moved to the LIMS watcher folder for verification and upload by the IM.

[Please note, the term EBF LIMS Integration is simply a 'placeholder name' in this research application build]
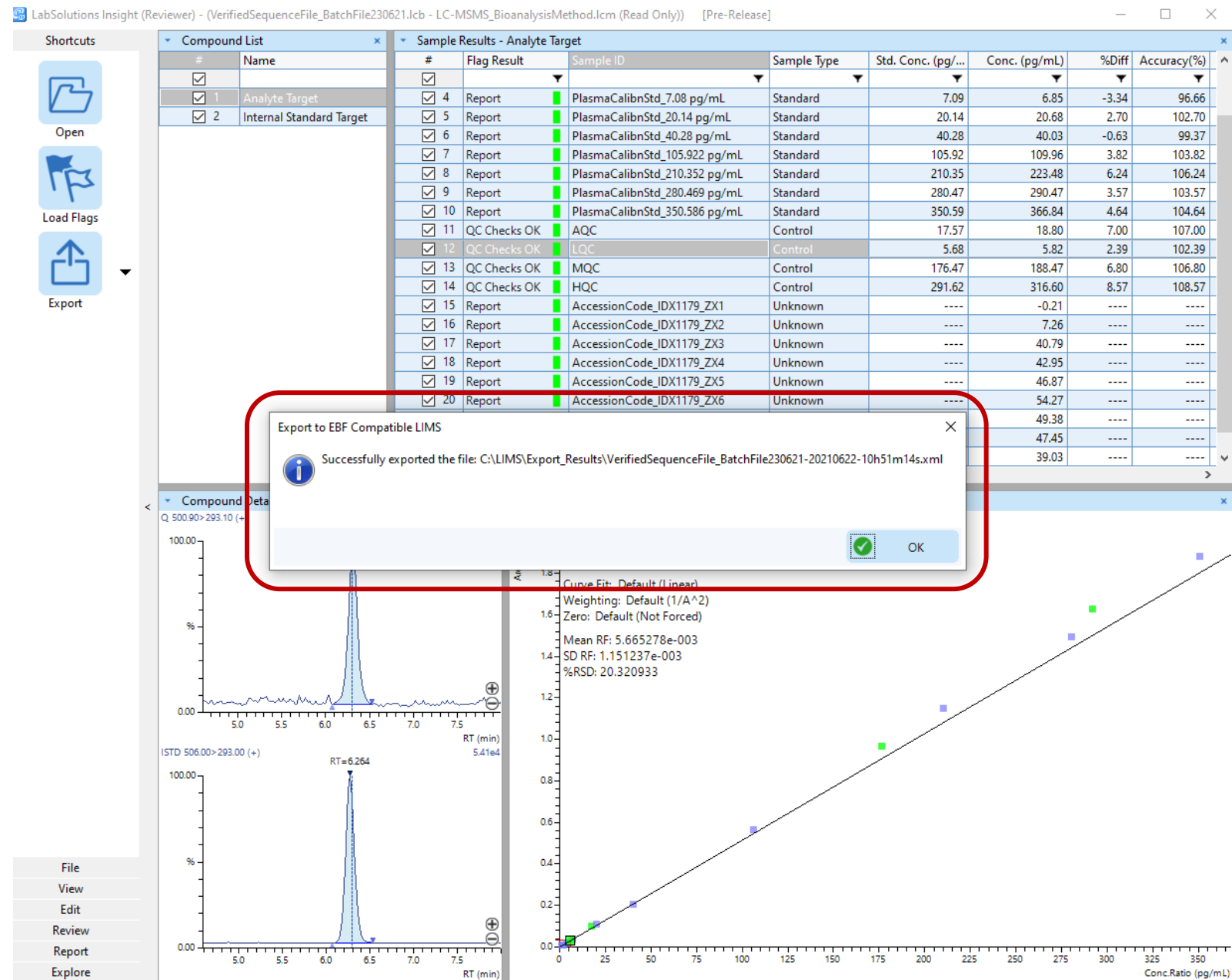
Step 3: Export Results (SCIEX)
Review data and convert results

A SCIEX application converts Analyst files into AnIML XML result files:

Analyst data files (.wiff): includes sample information, method information, technique information, spectra and chromatograms.

Results table (.rdb): includes the results table, integrated chromatograms and the audit trail for that results table.

Analyst audit trail (.ata, .atd): includes all audit records contained in the original files.
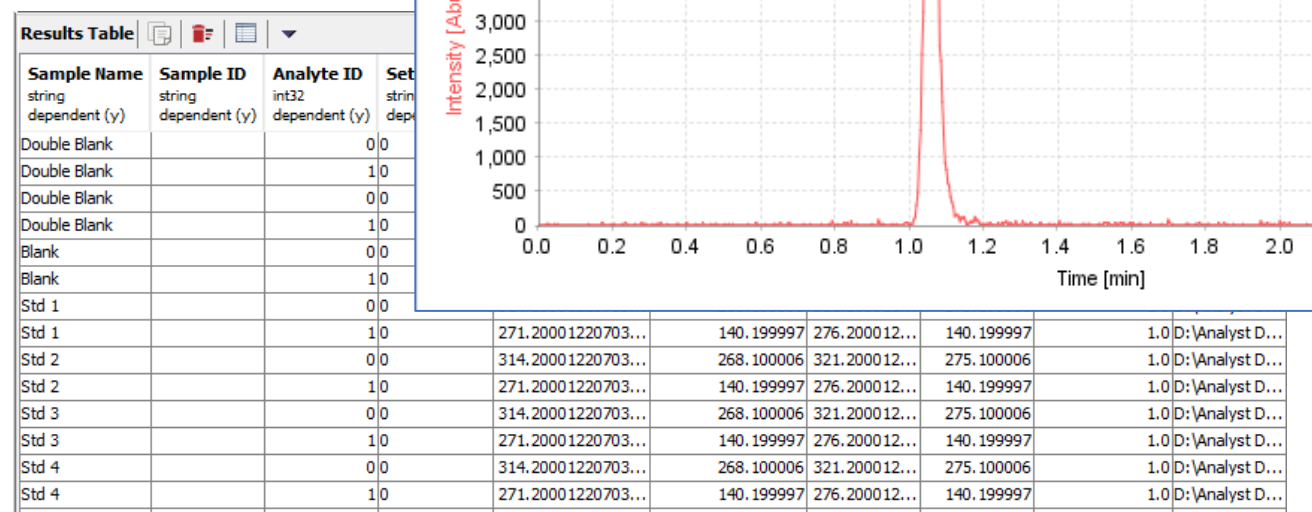
AnIML files converted by SCIEX software provide a complete and accurate representation of the original Analyst® data, including result table, chromatograms, method and audit trail.

Signature verification (SCIEX)
Verification of integrity

- A digital signature can be applied to each result file.

- Users can verify signature in a simple dialog

- Tamper evident – Users can check the digital signature status to determine if a file has been modified

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Step 4: Importing the Results back into the LIMS

The LIMS verifies the signed results file [**export.xml**], if valid, results are stored into the LIMS system

Importing an [export.xml] file in Watson LIMS™

In this screenshot, Watson LIMS users would simply choose a Run, click [Import] and select the [**export.xml**] file.

A Background process will verify the validity of the file using the submitter's public key.

Only validated files can be selected in the LIMS. Invalid files will go to a error-folder.

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Example

XML file containing analytical results

```xml
<?xml version="1.0"?>
- <AnIML>
    + <SampleSet>
    - <ExperimentStepSet>
        - <ExperimentStep Name="Bioanalysis" experimentStepID="e1">
            + <Method>
            - <Results Name="Analytical Result">
                - <SeriesSet Name="Results Table" length="48">
                    + <Parameter Name="Sample Name" seriesType="String" seriesID="s1" dependency="dependent">
                    + <Parameter Name="Analyte Name" seriesType="String" seriesID="s2" dependency="dependent">
                    + <Parameter Name="Concentration" seriesType="Float32" seriesID="s3" dependency="dependent">
                    + <Parameter Name="RT" seriesType="Float32" seriesID="s4" dependency="dependent">
                    + <Parameter Name="Area" seriesType="Float32" seriesID="s5" dependency="dependent">
                    + <Parameter Name="Area %" seriesType="Float32" seriesID="s6" dependency="dependent">
                    + <Parameter Name="Height" seriesType="Float32" seriesID="s7" dependency="dependent">
                    + <Parameter Name="Height %" seriesType="Float32" seriesID="s8" dependency="dependent">
                    + <Parameter Name="Concentration Ratio" seriesType="Float32" seriesID="s9" dependency="dependent">
                    + <Parameter Name="Area Ratio" seriesType="Float32" seriesID="s10" dependency="dependent">
                    + <Parameter Name="Height Ratio" seriesType="Float32" seriesID="s11" dependency="dependent">
                    + <Parameter Name="Internal Standard Name" seriesType="String" seriesID="s12" dependency="dependent">
                    + <Parameter Name="ISTD Concentration" seriesType="Float32" seriesID="s13" dependency="dependent">
                    + <Parameter Name="ISTD RT" seriesType="Float32" seriesID="s14" dependency="dependent">
                    + <Parameter Name="ISTD Area" seriesType="Float32" seriesID="s15" dependency="dependent">
                    + <Parameter Name="ISTD Height" seriesType="Float32" seriesID="s16" dependency="dependent">
                </SeriesSet>
            </Results>
        </ExperimentStep>
    </ExperimentStepSet>
    + <Signatures>
</AnIML>
```

Summary

What are the key advantages in this proposal

Data security is significantly increased

- The current data transfer cycle requires manual and time-consuming quality-control steps to mitigate the DI risks. In this proposal, the goal is to negate quality control steps and meet the need of health authorities DI expectations.

The technology is widely adopted and a vendor neutral solution

- The technology is open for all vendors to use and is intended as a generic solution.
- No bespoke interfaces required, reducing implementation and validation cost.
- The key point is that if anyone tampers or changes the sequence or export file the change is recorded. All tampered files are detected.
- Implementations from several key vendors demonstrate the feasibility

It is designed to make a near-zero impact on the current user experience

- The changes are all designed to work 'under the hood'
- In this proposal the fundamental point is the data security is managed by the software and is not exposed to the user.

Discussion

How to move this forward as a way to improve data security, helping regulatory audits and creating a standard for moving data between a LIMS and LC-MS

- As with all changes, **we need 'buy-in'** from pharma companies for regulated bioanalysis
- To accelerate this change the quicker the 'buy-in', the quicker a product can be created.
- The 'buy-in' applies to:
    - pharma companies
    - regulators
    - partner consortia (AAPS)
    - more vendors

Going forward….

- Options for a 'Working Group' to consider expanding domain into other assays / techniques
- Future: file-less options

Opportunity to join

- We are looking to create a **group of early adopters** to deploy and refine the approach

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Acknowledgements

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