Time to bring it all together

From data transfer to processing to full reporting under ICH M10 based on the EBF Data Integrity Initiative (LCMS)

14th EBF-Open Symposium, Barcelona 2021, Norbert Bittner

up to data

EBF initiative 2019/2020

Presented at the 13th EBF Open Symposium
E-environment/Data Integrity Workshop

Data Integrity Workshop

13th EBF Open Symposium

E-Environment; towards a vendor neutral bi-directional data transfer process

Gidion de Boer, Neil Loftus, Burkhard Schaefer (on behalf of the working group)

Following the EBF 2019 workshop the White Paper was published in Bioanalysis

White Paper

Bioanalysis

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

Cecilia Arfvidsson[1], David Van Bedaf[2], Susanne Globig[3], Magnus Knutsson[4], Mark Lewis[5], Stuart McDougall[6], Marco Michi[7] & Philip Timmerman*[,8]

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The White Paper was published online 22 July 2020 and highlighted the need to increase compliance related to data integrity (DI) in todays LC-MS workflows **(Bioanalysis (2020) 12(14), 1033–1038)**

https://bcn.e-b-f.eu/wp-content/uploads/2020/12/230.-Gidion-de-Boer-Neil-Loftus-Burkhard-Svchaefer.pdf

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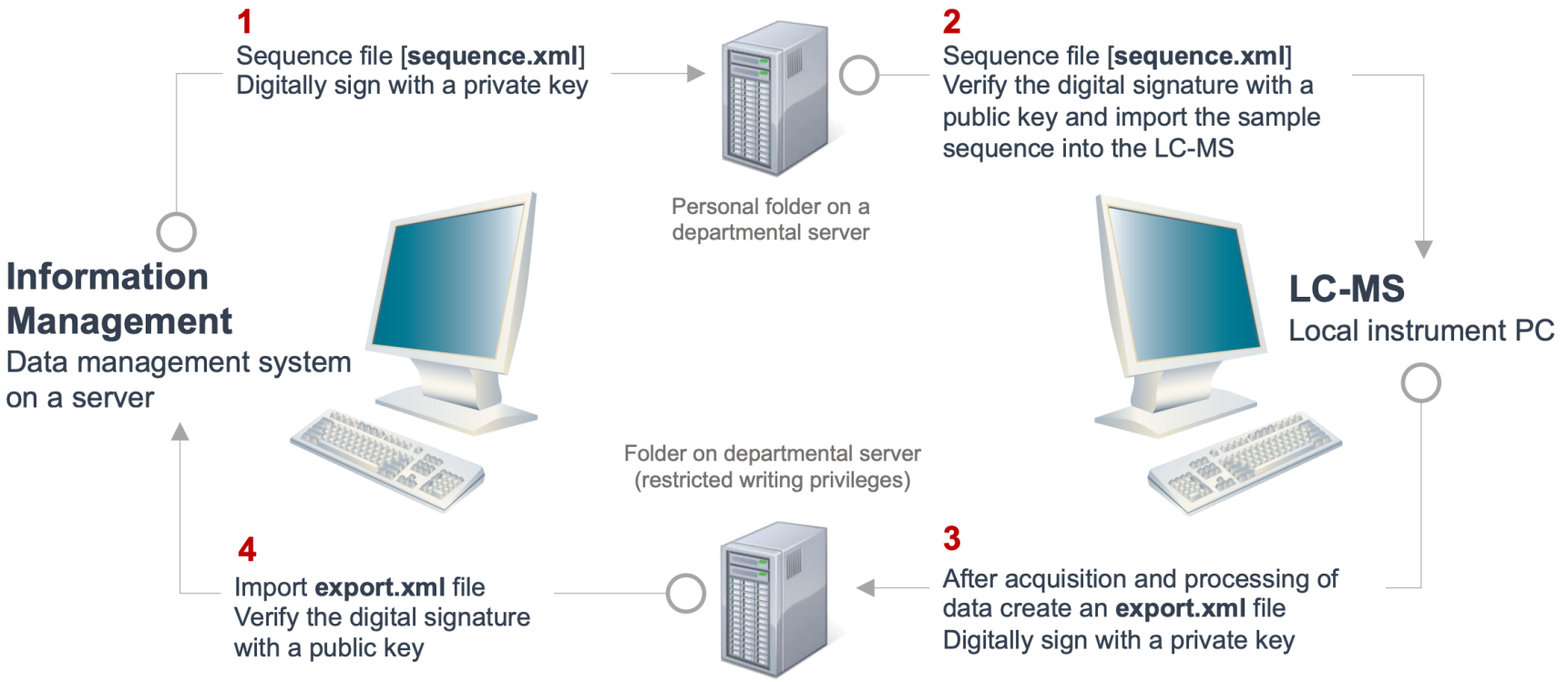
The scope: Data-Integrity for LIMS to/from LCMS workflow

Presented at the 13th EBF Open Symposium
E-environment/Data Integrity Workshop

A proposed way forward

Replacing .txt files with digitally signed .xml files



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up to data

SCIEX: Data format comes to life

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Keystone™ software: your SCIEX data in a single, vendor-neutral format that is secure, open and sharable

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Your company may be generating large amounts of analytical data from many different types of analytical instrumentation, from a wide variety of instrument vendors. Viewing this stored data, each in a distinct proprietary data format, requires an ever-growing list of application and operating system software. Many research organizations are developing informatics solutions based on vendor-neutral data formats to address this challenge.

SCIEX Keystone software provides tools to enable these informatics workflows, providing data storage and display of your SCIEX nominal mass data in the open, vendor-neutral AnIML file format.

The AnIML file format is an analytical data standard developed by ASTM International that can be used to store data from different analytical instruments in an open XML-based format. SCIEX has adopted this open standard to help you increase the utility of your SCIEX mass spectrometry data.

Keystone Converter Software will allow you to convert the following SCIEX data into the AnIML format:

- Analyst™ Software nominal mass data files (wiff): includes sample information, method information, technique information, spectra and chromatograms.
- Results table (.rdb): includes the results table, all chromatograms and the audit trail for that results table.
- Analyst Software audit trail (.ata, .atd): includes all the audit records contained in the original files.

Keystone also offers digital signatures for data integrity and security.

https://sciex.com/products/software/keystone-software, May 2021

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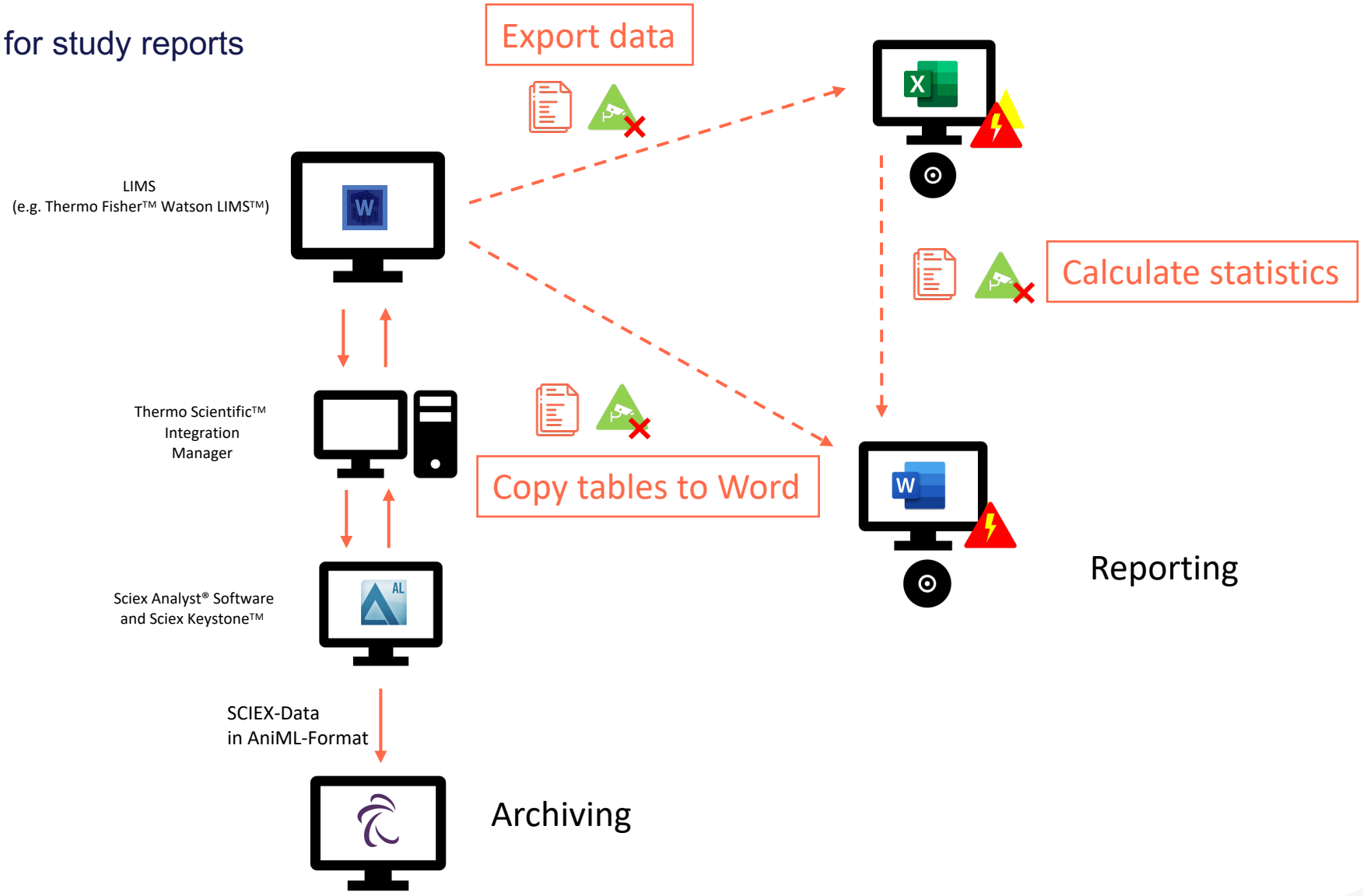
Reporting – still an open DI-issue in a LIMS scenario

- Data-Integrity issues for study reports



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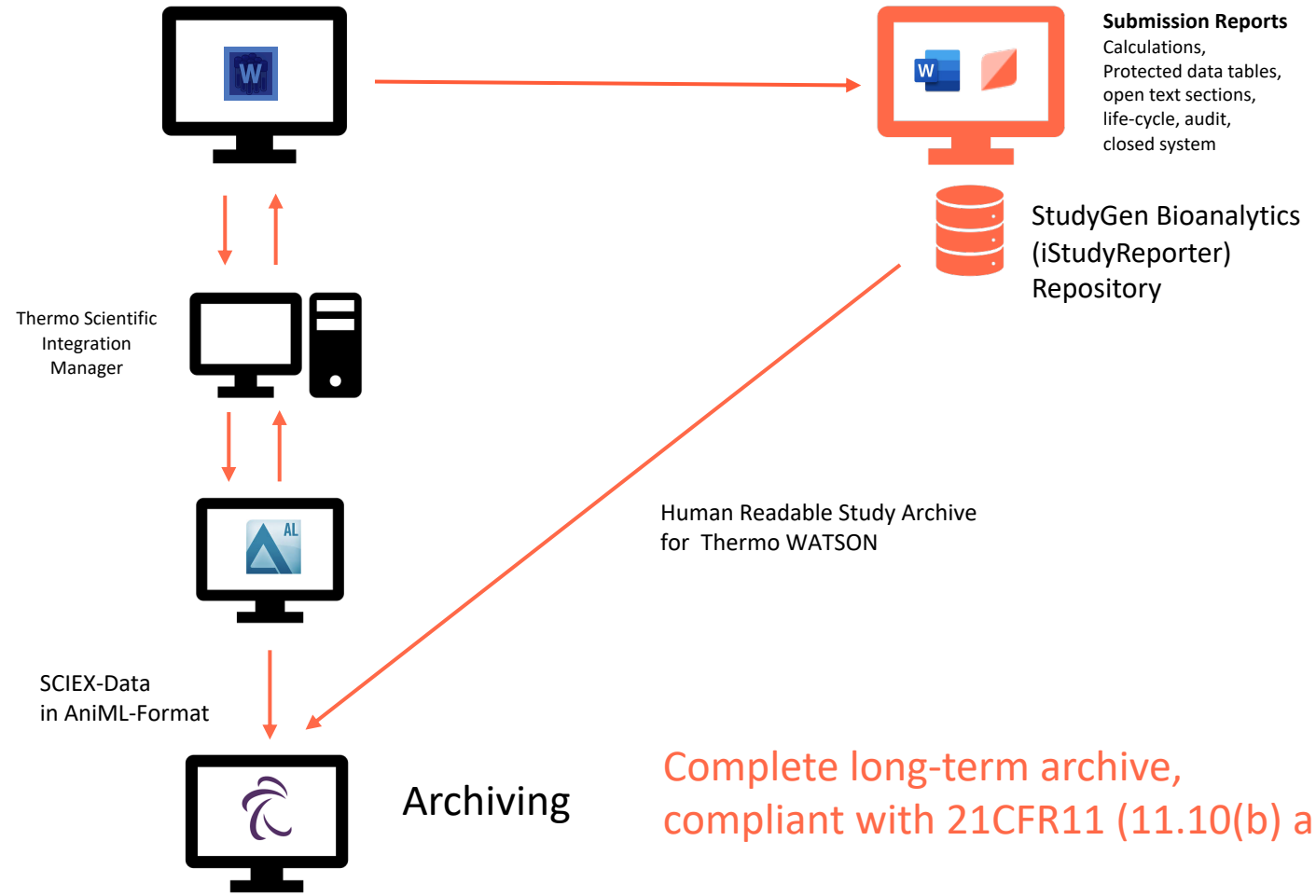
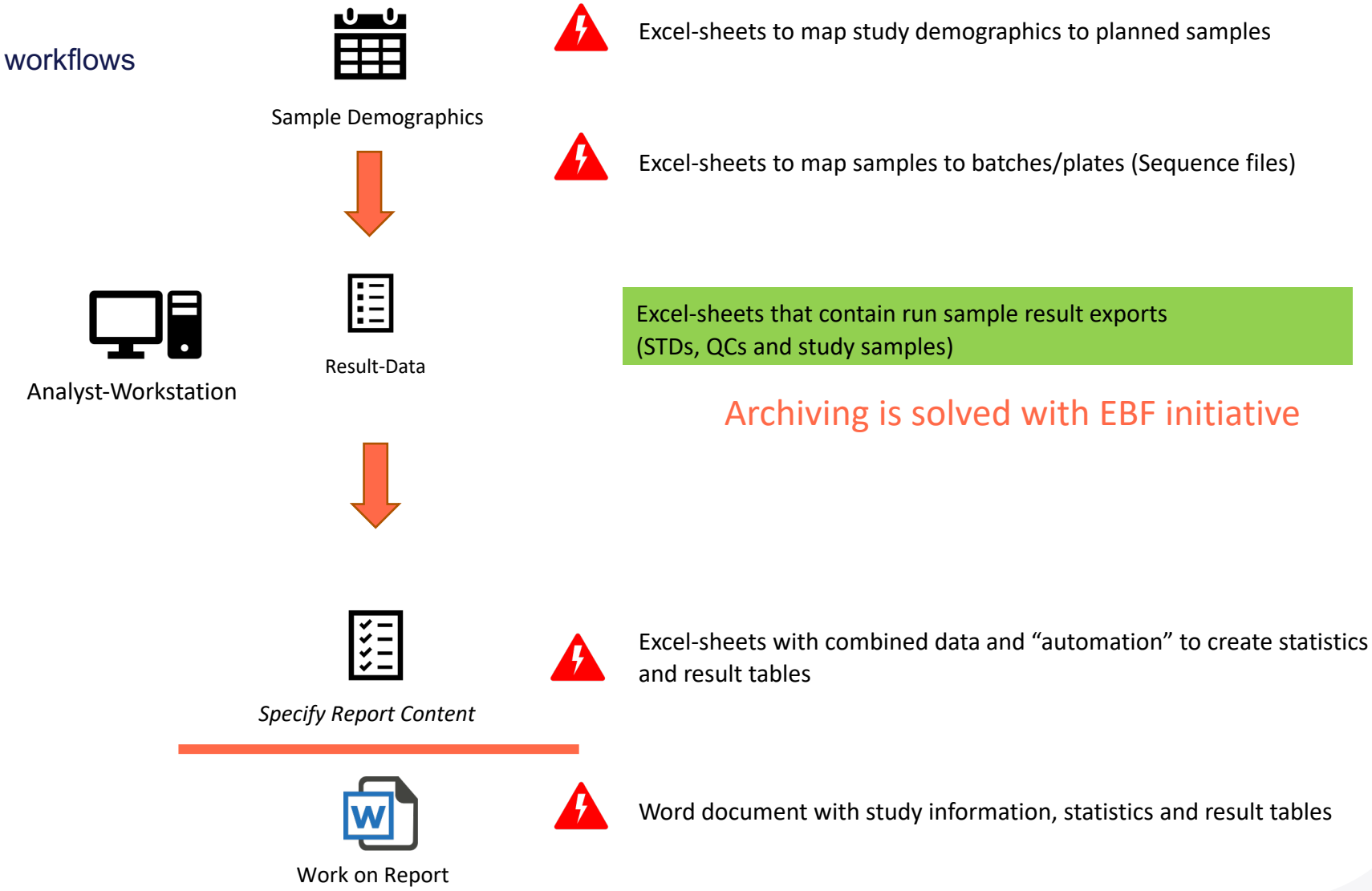
Reporting DI-Issues in this scenario solved by commercial products

- Data-Integrity issues for study reports, solved e.g. with StudyGen (former iStudyReporter)



Data Integrity issues in a none-LIMS scenario

- Current state:
  - Word/Excel dominated workflows



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Project to resolve this situation

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- Based on up to data application prototype

- Joint project of Idorsia (Susan Globig) and up to data initiated mid-2021

- Goals:
  - Introduce data integrity measures in a none-LIMS scenario
  - Introduce and support standardized workflows
  - Allow to instantly generate submission-ready bioanalytical reports without further QC measures
  - Incorporate ICH M10 requirements for reporting as they will come available
  - Provide a GLP compliant application

- Approach:
  - Take advantage of the features of the commercially available SCIEX data converter
  - Leverage and extend functionality of existing application
  - Use state-of-the-art cloud technology
  - Evaluate approaches for private and public cloud deployment

- Expectation:
  - Reduce the time and effort required to manually perform quality control of LCMS data
  - Reduce the time to create, review and submit bioanalytical reports

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None-LIMS scenario workflow

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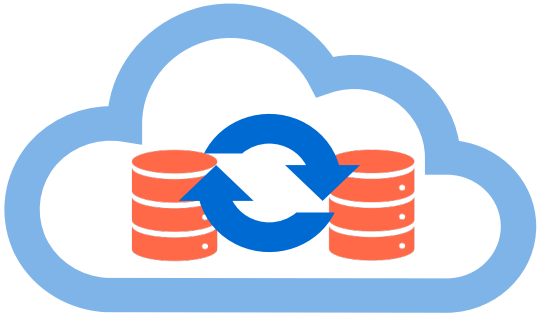
Upload Excel-Sheet containing sample-ids and sample specifics of study (Gender, Age, Dosage, …)

Sample Demographics

Analyst-Workstation

Sequence-Files
Result-Data



Review

Cloud-based management of study data and reports

Web-App

Specify Report Content

Work on Report

up to data

None-LIMS scenario workflow

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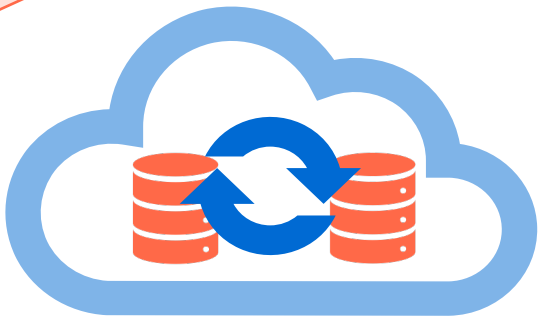
Upload
EBF AniML-Files
or
Sciex native WIFF, RDB files

Sample Demographics

Analyst-Workstation

Sequence-Files
Result-Data



Review

Cloud-based management of study data and reports

Web-App

Specify Report Content

Work on Report

up to data

None-LIMS scenario workflow

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Perform “Data Review”
based on
FDA Guideline for Run Acceptance
Best practice

Sample Demographics

Analyst-Workstation

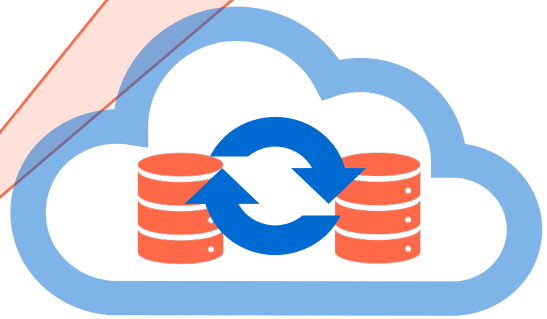
Sequence-Files
Result-Data

Review

Web-App

Specify Report Content

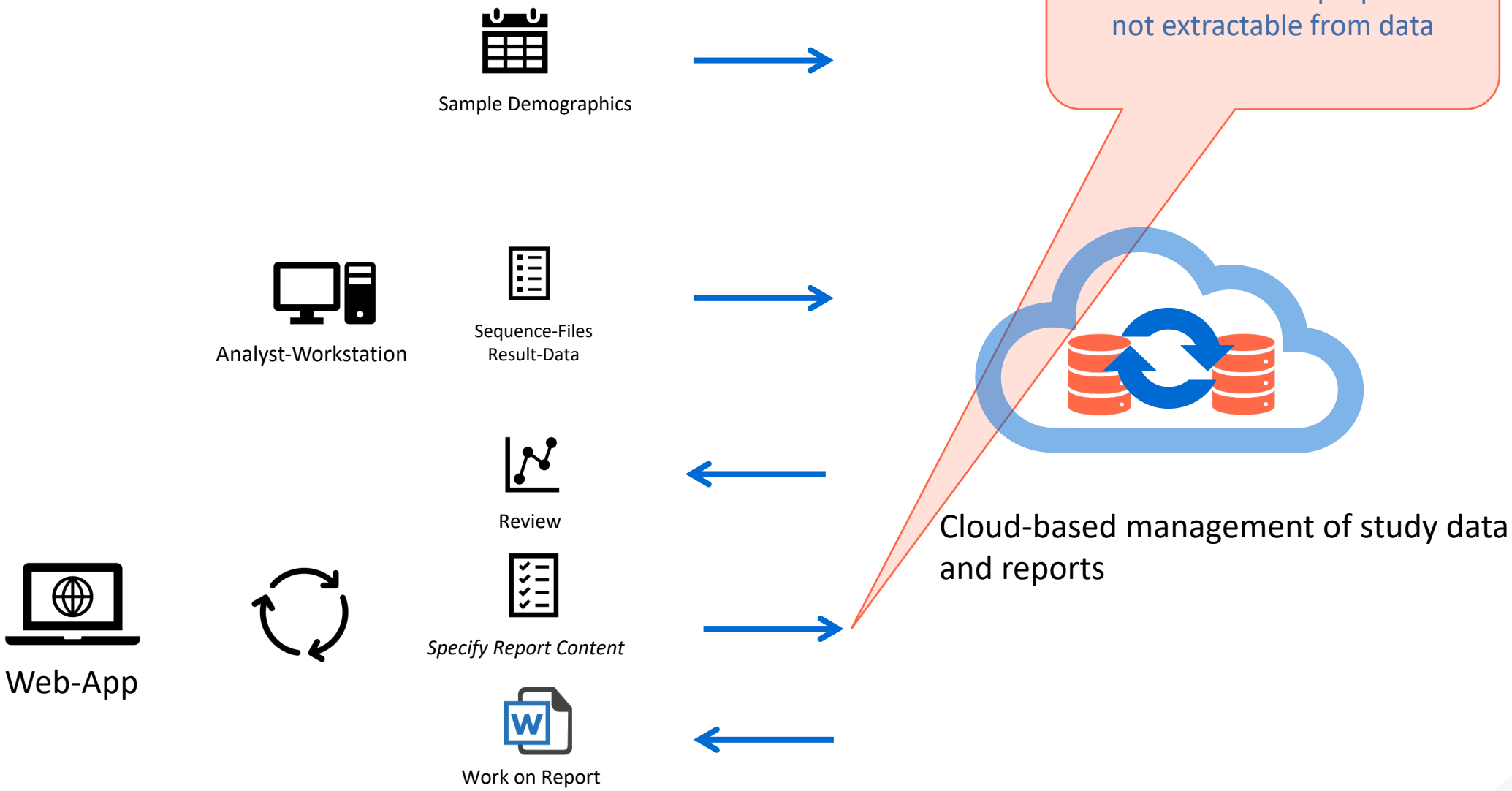
Work on Report



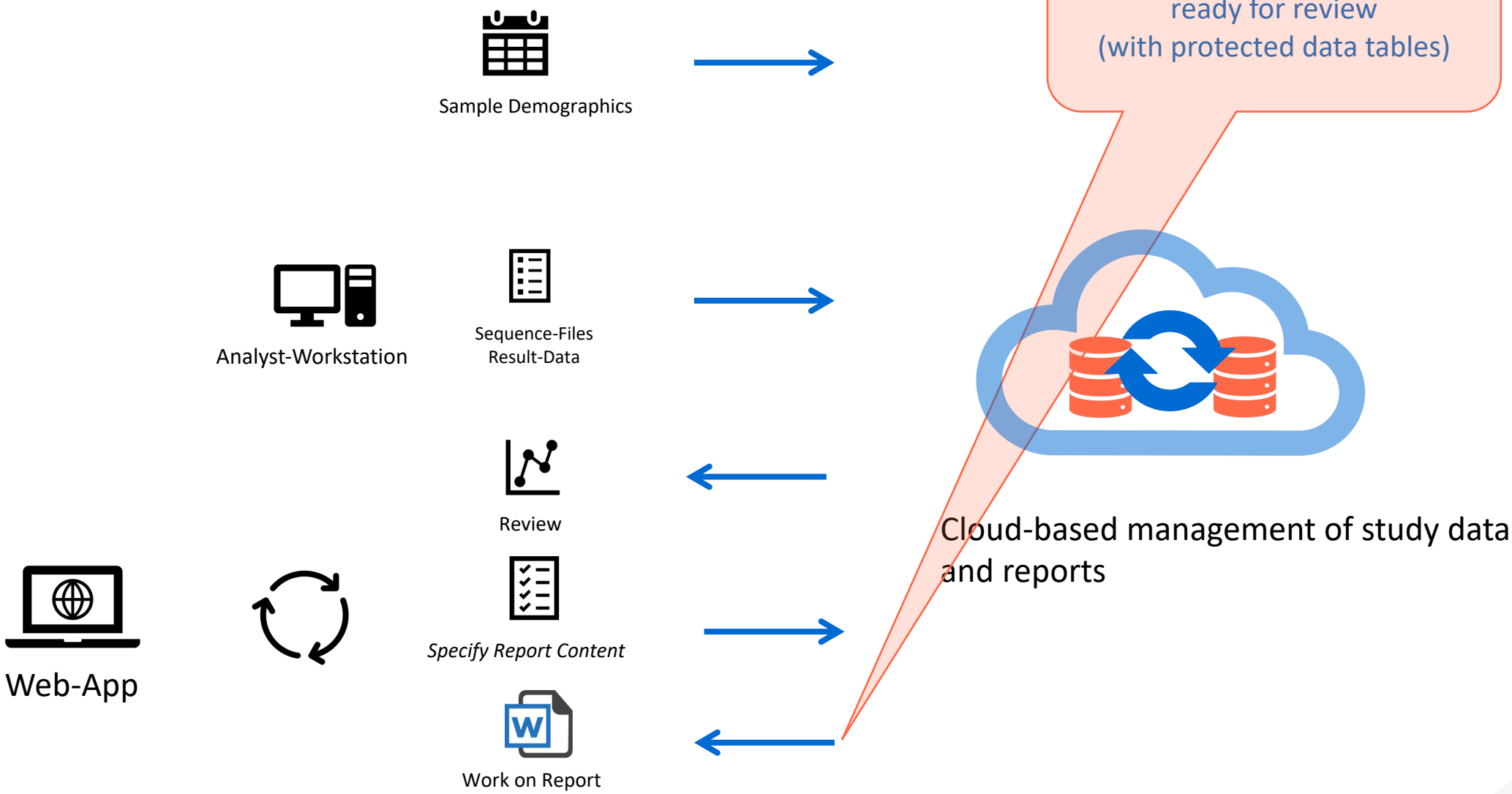
Cloud-based management of study data and reports

up to data

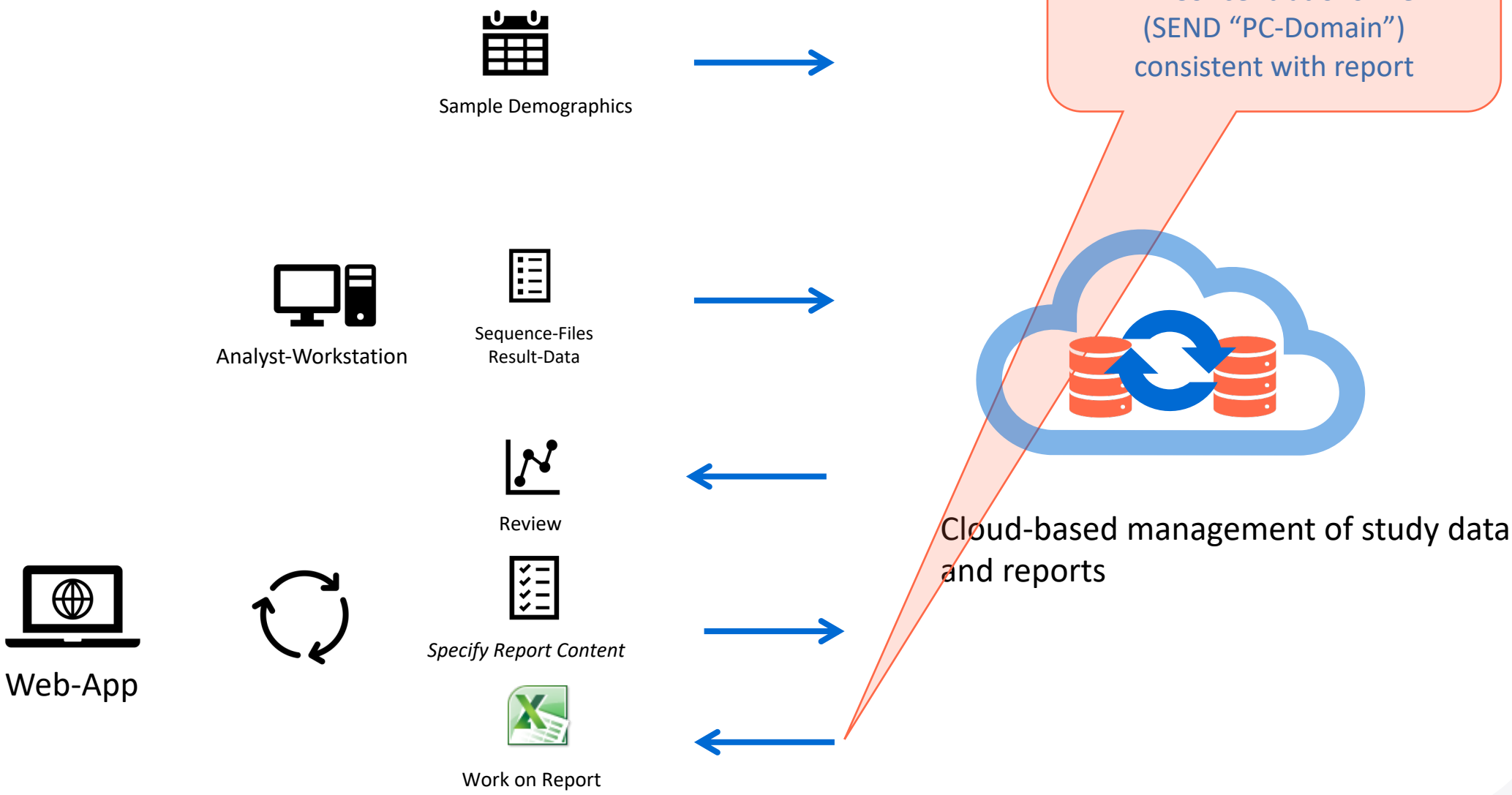
None-LIMS scenario workflow



None-LIMS scenario workflow



None-LIMS scenario workflow



Technological and workflow challenges

- Technological challenges
  - Selection of technology for efficient implementation
    - Rejected container approach
    - Serverless architecture
  - Transfer/Migration of existing software modules and algorithms
    - No one-to-one migration of current solution
    - Modularization and migration to serverless architecture
  - Initial feasibility study by up to data in 2021, to leverage future proof technologies

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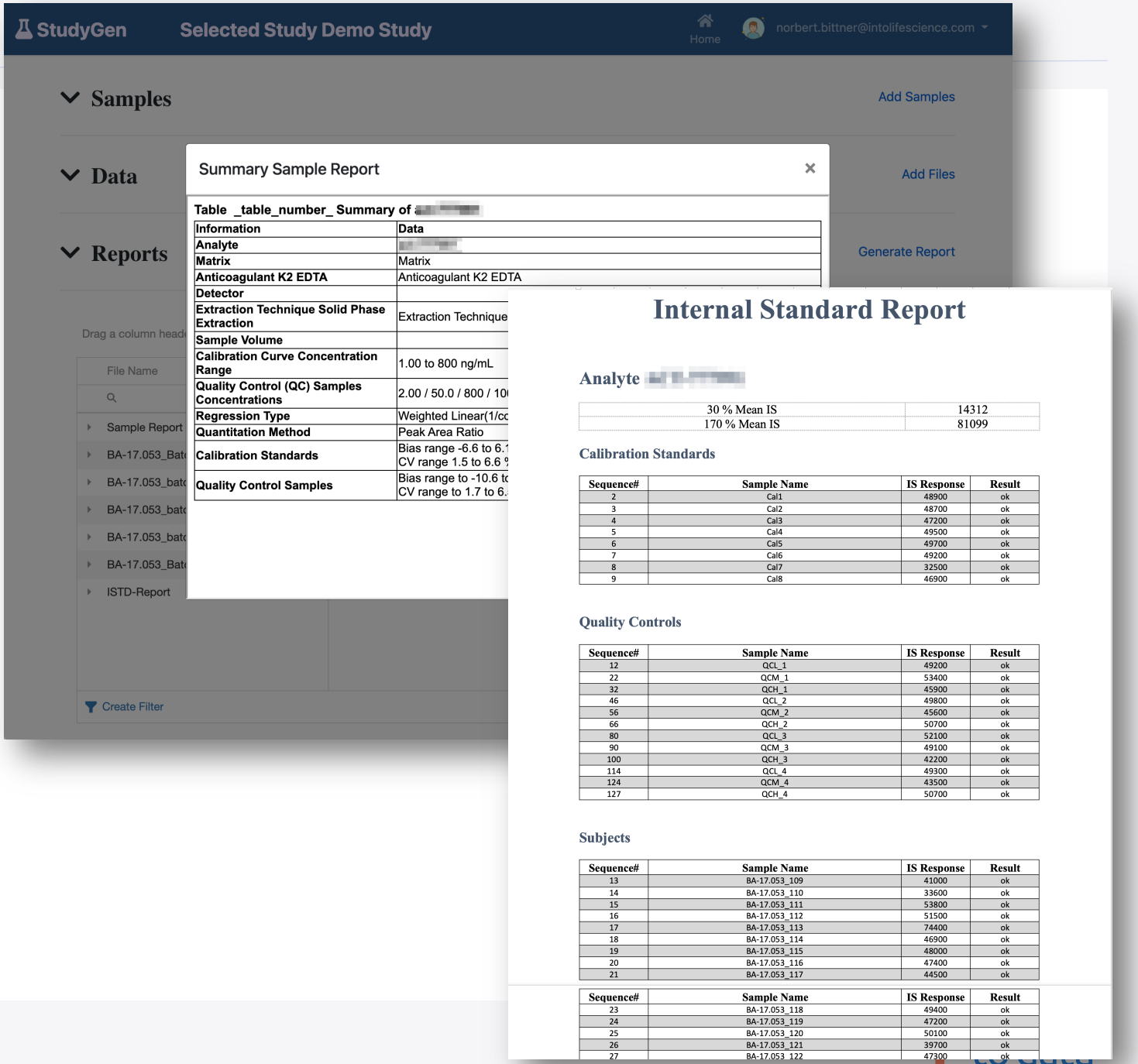
- Open workflow challenges
  - Setup of specific workflows to support
    - Re-assay decisions
    - Incurred sample reanalysis

Regulatory Challenges

- Build „compliant“ bioanalytical reports
  - Best practice based on reports of existing clients
  - Take available guidelines into account
    - FDA
      - Bioanalytical Method Validation, Guidance for Industry (May 2018)
      - Bioanalytical Methods Template, Guidance for Industry, Tech. Specifications Document (Sep 2019)
    - EMA
      - Guideline on bioanalytical method validation (Feb 2012)
    - ICH (draft)
      - Bioanalytical Method Validation M10 (draft, Feb 2019)
      - …. expected to change
  - Enable configuration of templates
- Interpret applicable GxP regulations in a serverless architecture
  - e.g. how to interpret “Installation Qualification” or “multi tenant”
- Implications of “Software as a Service” (SaaS) for a regulated laboratory
  - e.g. how to define ”control of data” or validate application updates
  - What does “disaster recovery” mean in an “AWS Availability Zone”

Where are we now?

- Prototype is implemented
  - AWS-based, serverless architecture
- Initial Report templates are setup
  - IS-Analysis based on raw data
  - Bioanalytical Study Report
- Development of regulatory framework supported by
  - Bob McDowall
  - Practical experience of Idorsia („Cloud-first approach“, see https://aws.amazon.com/solutions/case-studies/idorsia-case-study/)



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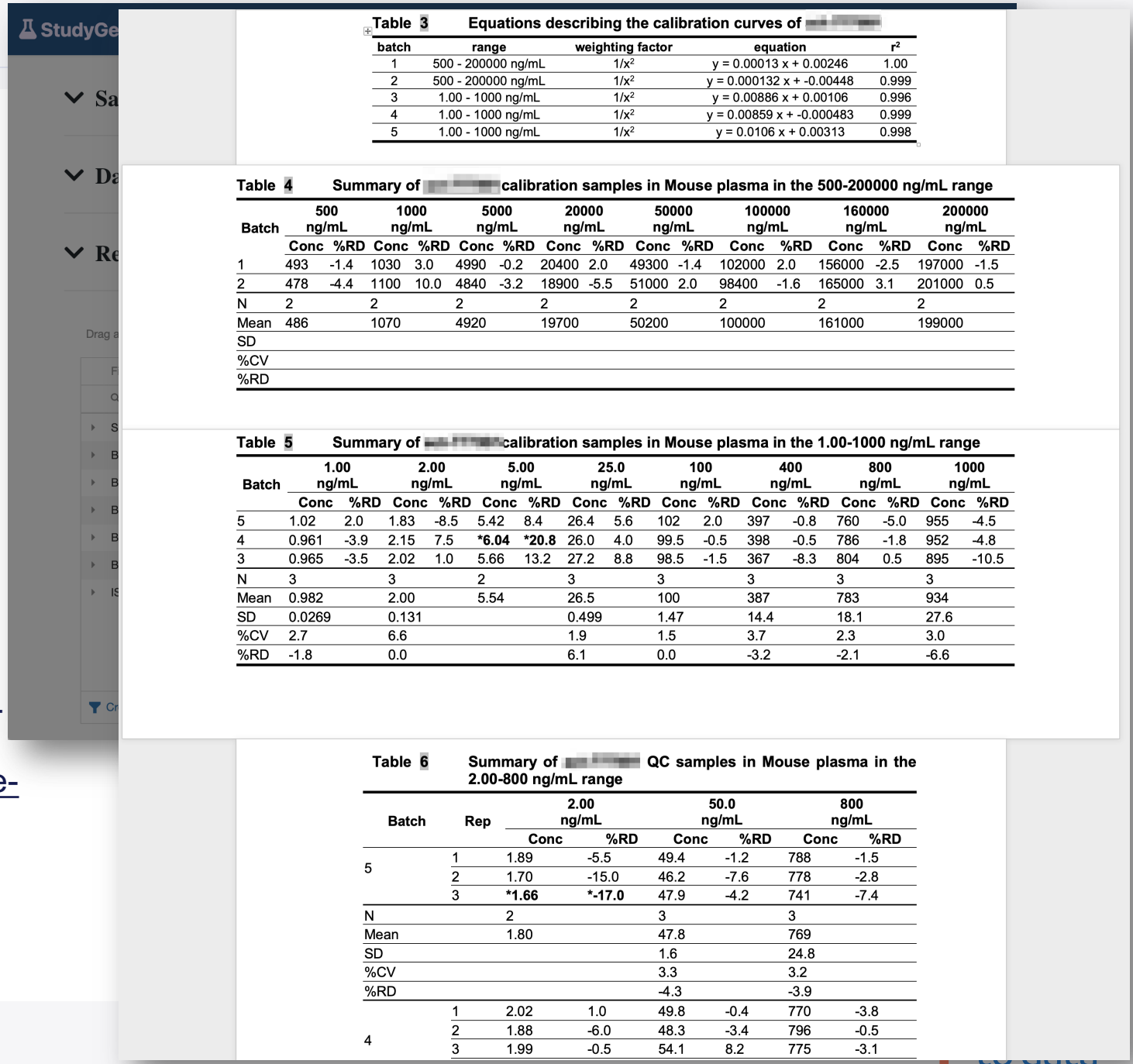

Table 3 Equations describing the calibration curves of [redacted]

batch	range	weighting factor	equation	r^2
1	500 - 200000 ng/mL	$1/x^2$	y = 0.00013 x + 0.00246	1.00
2	500 - 200000 ng/mL	$1/x^2$	y = 0.000132 x + -0.00448	0.999
3	1.00 - 1000 ng/mL	$1/x^2$	y = 0.00886 x + 0.00106	0.996
4	1.00 - 1000 ng/mL	$1/x^2$	y = 0.00859 x + -0.000483	0.999
5	1.00 - 1000 ng/mL	$1/x^2$	y = 0.0106 x + 0.00313	0.998

Table 4 Summary of [redacted] calibration samples in Mouse plasma in the 500-200000 ng/mL range

Batch	500 ng/mL		1000 ng/mL		5000 ng/mL		20000 ng/mL		50000 ng/mL		100000 ng/mL		160000 ng/mL		200000 ng/mL	
	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD
1	493	-1.4	1030	3.0	4990	-0.2	20400	2.0	49300	-1.4	102000	2.0	156000	-2.5	197000	-1.5
2	478	-4.4	1100	10.0	4840	-3.2	18900	-5.5	51000	2.0	98400	-1.6	165000	3.1	201000	0.5
N	2		2		2		2		2		2		2		2	
Mean	486		1070		4920		19700		50200		100000		161000		199000	
SD																
%CV																
%RD																

Table 5 Summary of [redacted] calibration samples in Mouse plasma in the 1.00-1000 ng/mL range

Batch	1.00 ng/mL		2.00 ng/mL		5.00 ng/mL		25.0 ng/mL		100 ng/mL		400 ng/mL		800 ng/mL		1000 ng/mL	
	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD	Conc	%RD
5	1.02	2.0	1.83	-8.5	5.42	8.4	26.4	5.6	102	2.0	397	-0.8	760	-5.0	955	-4.5
4	0.961	-3.9	2.15	7.5	***6.04**	***20.8**	26.0	4.0	99.5	-0.5	398	-0.5	786	-1.8	952	-4.8
3	0.965	-3.5	2.02	1.0	5.66	13.2	27.2	8.8	98.5	-1.5	367	-8.3	804	0.5	895	-10.5
N	3		3		2		3		3		3		3		3	
Mean	0.982		2.00		5.54		26.5		100		387		783		934	
SD	0.0269		0.131				0.499		1.47		14.4		18.1		27.6	
%CV	2.7		6.6				1.9		1.5		3.7		2.3		3.0	
%RD	-1.8		0.0				6.1		0.0		-3.2		-2.1		-6.6	

Table 6 Summary of [redacted] QC samples in Mouse plasma in the 2.00-800 ng/mL range

Batch	Rep	2.00 ng/mL		50.0 ng/mL		800 ng/mL	
		Conc	%RD	Conc	%RD	Conc	%RD
5	1	1.89	-5.5	49.4	-1.2	788	-1.5
	2	1.70	-15.0	46.2	-7.6	778	-2.8
	3	***1.66**	***-17.0**	47.9	-4.2	741	-7.4
N		2		3		3	
Mean		1.80		47.8		769	
SD				1.6		24.8	
%CV				3.3		3.2	
%RD				-4.3		-3.9	
4	1	2.02	1.0	49.8	-0.4	770	-3.8
	2	1.88	-6.0	48.3	-3.4	796	-0.5
	3	1.99	-0.5	54.1	8.2	775	-3.1

Coming up next

- Develop deployment strategy for “private and public” cloud that meets GLP requirements
- Test phase with other use-cases (Immunogenicity, Biomarker, …) and testers (Pharma, CROs) planned for Q1/2022
- Go-live of Idorsia planned for Q2/2022

Summary

- EBF initiative solves DI issues in data transfer from/to LCMS and other devices
  - Focus on LIMS
  - Long-Term archiving in vendor neutral format

- Challenge remains for none-LIMS scenario

  - Data processing is major issue here, otherwise solved with LIMS

  - EBF initiative builds a foundation to bring it all together
    - Leverage “secure” raw data files
    - Build cloud-based technology
    - Provide upcoming regulatory framework
    - Leverage available guidelines on content of reports for this environment (ICH M10)

Acknowledgements

- Acknowledgements

  - Idorsia
    - Susan Globig
    - Joel Arida
    - Jean-Maxime Pommery

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    - Bob McDowall

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    - Lars Schröder
    - Henry Springer

  - into Life Science
    - Jay Cheruvelil
    - Shehroze Malik
    - Usman Chaudhary

Thank you for your attention

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