

Introducing Laboratory Automation to Regulated Bioanalysis

Integration of Liquid Handlers to a Paperless Laboratory



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A Few General Considerations

Lab automation is commonly used in clinical routine laboratories for standard demands:

- High sample numbers on many analytes
- Day-in, day-out the same analysis
- Out-of-the-box kits, very few modifications
- Almost no in-house methods on these systems



In Pharma, in-house analysis is performed with robotic systems, if/since projects are scheduled for long periods and outsourcing is not foreseen

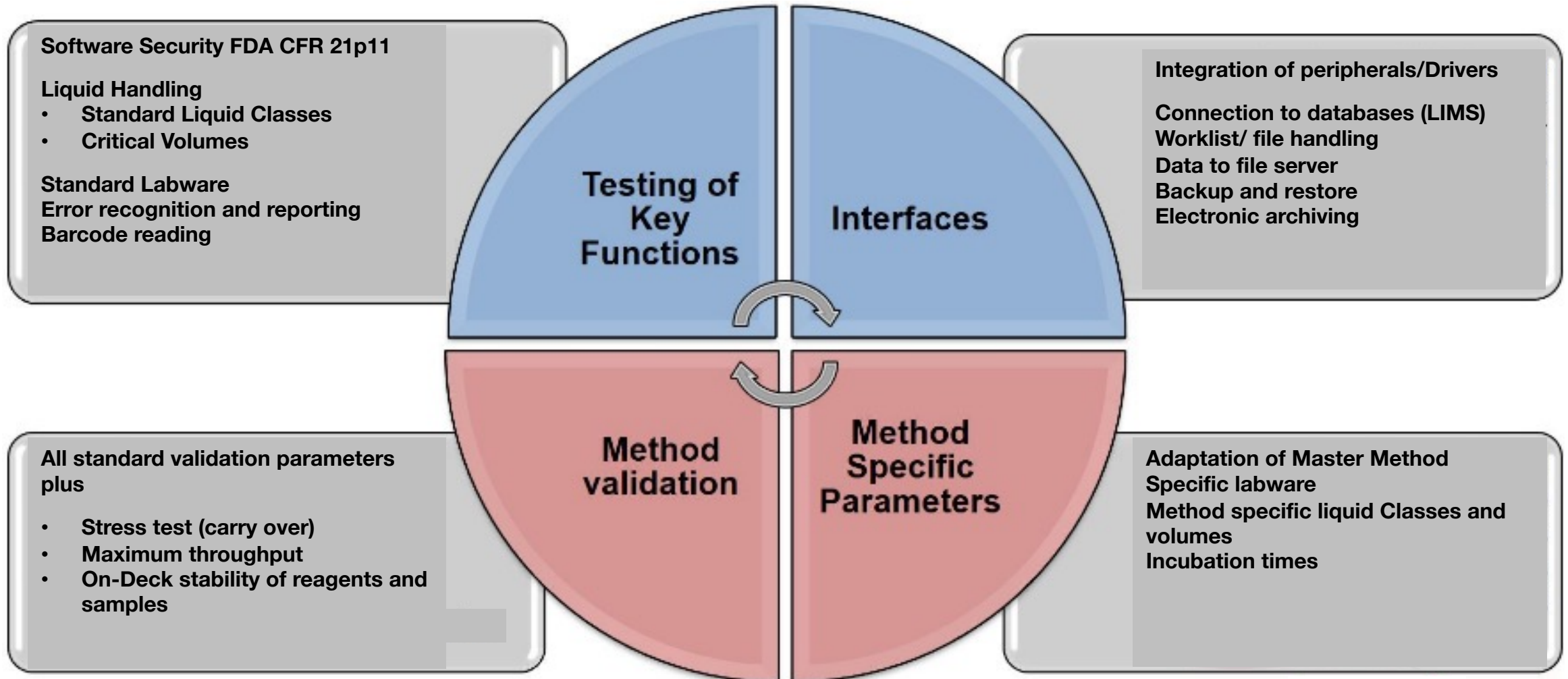
- High sample number on few analytes
- Day-in, day-out the same analysis
- In-house methods, very few modifications

But how to automate in CROs, with short to midterm projects, sample numbers/study 100-5000?

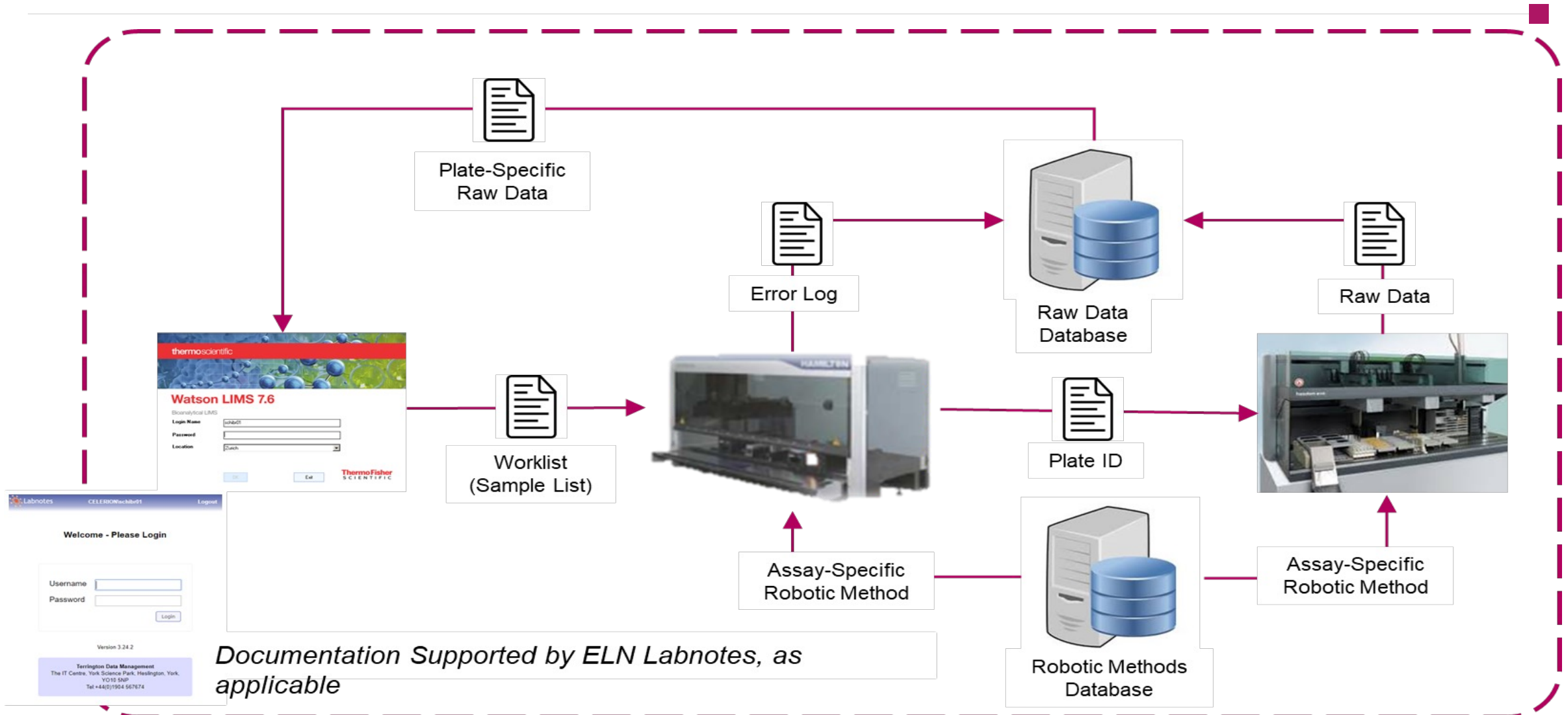
Desired Achievements

- ✓ Increased throughput, especially for new/less experienced lab technicians
- ✓ Optimization of resources: technicians get available for other tasks, while machine is running (e.g. documentation, planning, data evaluation)
- ✓ Traceability of data: Worklist driven processes, barcode comparison and system log/trace files avoid errors and allow for detailed explanation of any events.
- ✓ Customized output files compile relevant information → study documentation
- ✓ Assay robustness: exclusion of human factors produce analytical data like on the «copy machine», Repetitions and incurred sample reproducibility at highest level
- ✓ Reproducibility of results: assay transfer between laboratories shows higher agreement when automated methods are used than manual methods (especially for transfer between RnD and GxP laboratories)

Automation Validation Approach – Prove Suitability for Intended Use



Data Flow: Connection Between Robots, LIMS and ELN



Routine Checks With Associated Documentation in the ELN Labnotes

Attachments (5)
Attachments (5)

Equipment Recurring Task

Celerion - FZRH\SOP.13002-01 Equipment Recurring Task (Version 02)

ID: *Performed Date:

Check Tasks Performed

- PM
- PQ
- NIAP
- NIAP
- NIAP

Details

*Describe Details:

Equipment / Components Used to Performed Task:

Results

*Task Pass / Fail Status:

*Results Details:

*SoftMax Results printed into .pdf file: .pdf need to be created before signing "Compiled by"

*Location of Supporting Documentation:

Equipment Status

Following Recurring Task(s) needs to be Performed:

Equipment Tagged "Out of Service":

*Compiled by:

*Reviewed for Completeness and Correctness by:

Equipment Non-Recurring Task

Celerion - FZRH\SOP.13002-02 Equipment Non-Recurring Task (Version 02)

ID:

*Task: *Out of Service Date:

Details

*Reason:

*Location of Supporting Documentation:

Equipment Status

Equipment Tagged "Out of Service": *Approx. Out of Service Time:

5 Aug 2020 11:49 (UTC+2) (CELERION\groesm01): connection issue might be a consequential error of unplugging and cleaning washer and LPR240 the week before. TAKE CARE OF CABLE CONNECTIONS

*Compiled by:

*Reviewed for Completeness and Correctness by:

Tecan Freedom EVO PQ

Celerion - FZRH\SOP.40015-01 Tecan EVO PQ (Version 12)

PQ ID:

*Performed Date: *PQ: Equipment ID:

Start Up / Shut Down / Daily Maintenance as per SOP Performed

*Microtiter Plate:

*No. of Wells Aliquoted:

*Test Solution:

Balance:

*Microplate Reader:

*Volume 01 (mL)	0.250
*Volume 02 (mL)	0.050
*Weight of Empty Plate (g)	48.485000
*Weight of Full Plate with Volume 01 (g)	58.358000
*Weight of Full Plate with Volume 01 and 02 (g)	60.794000
Accuracy Volume 01 (%)	98.9
Accuracy Volume 01 Pass / Fail Status	Pass
Accuracy Volume 02 (%)	101.5
Accuracy Volume 02 Pass / Fail Status	Pass
*Precision Pass / Fail Status	Pass

Acceptance Criteria

- * Accuracy (%): Between 98.0% - 102.0%
- * Precision (CV %): Less or equal to 2.0%

PQ Pass / Fail Status: PQ Due Date:

*Performed by:

*Reviewed for Completeness and Correctness by:

Assessment for Failed Qualification Tasks

Action:

Comments:

Approved by (System Owner):


Routine Checks With Associated Documentation in the ELN Labnotes

Please select balance

Tecan Freedom EVO PQ
Celerion - FZRH SOP.40015-01 Tecan EVO PQ (Version 12)

PQ ID:

***Performed Date:** ***PQ:** **Equipment ID:**



Start Up / Shut Down / Daily Maintenance as per SOP Performed

***Microtiter Plate:**

***No. of Wells Aliquoted:**

***Test Solution:**

Balance:

***Microplate Reader:**

*Volume 01 (mL)	0.250	
*Volume 02 (mL)	0.050	
*Weight of Empty Plate (g)		📌
*Weight of Full Plate with Volume 01 (g)		📌
*Weight of Full Plate with Volume 01 and 02 (g)		📌
Accuracy Volume 01 (%)		
Accuracy Volume 01 Pass / Fail Status		☰
Accuracy Volume 02 (%)		
Accuracy Volume 02 Pass / Fail Status		☰
*Precision Pass / Fail Status		☰

Acceptance Criteria

* Accuracy (%): Between 98.0% - 102.0%

* Precision (CV %): Less or equal to 2.0%

PQ Pass / Fail Status:

PQ Due Date:

***Performed by:**

***Reviewed for Completeness and Correctness by:**

Development of Automated Methods, Testing and Release

The image displays three sequential screenshots of the 'Liquid Handling Robotic Methods Change Control' software interface, illustrating the process from request to release.

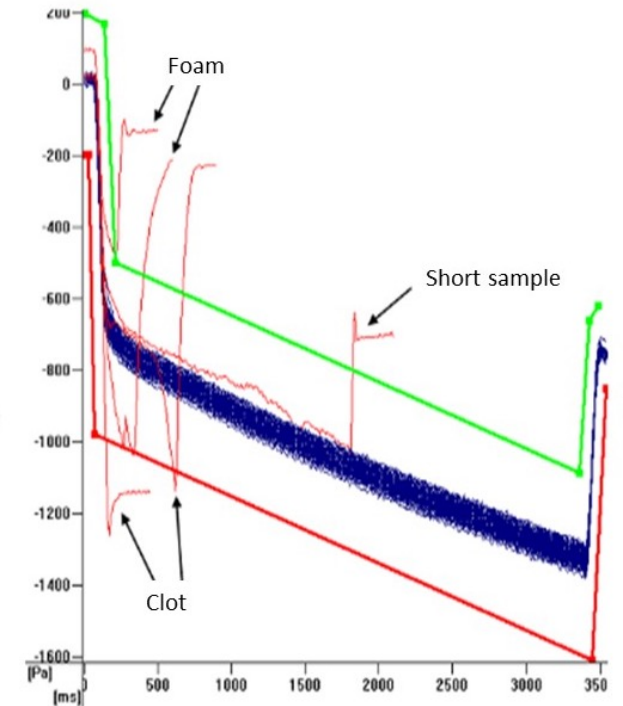
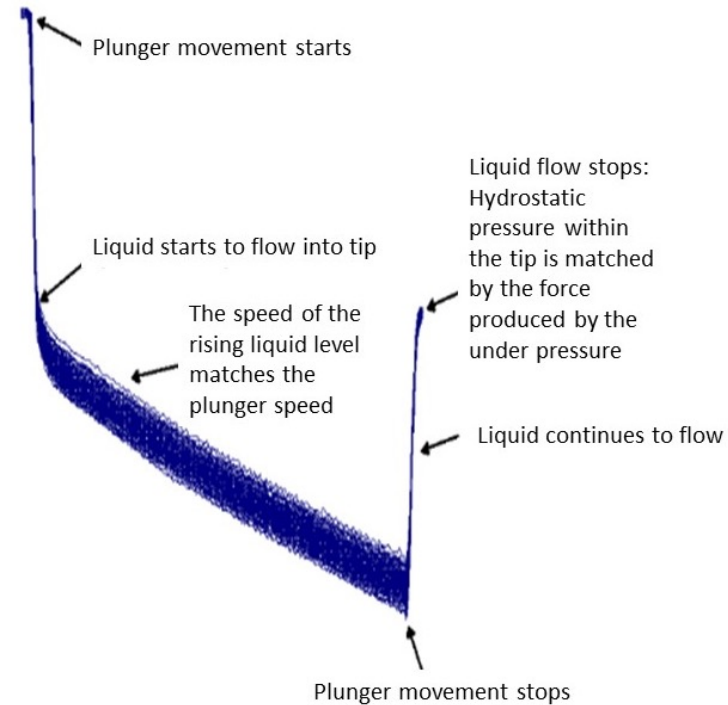
- Left Screenshot (Request):** Shows a 'Request Type' of 'New' and 'Current Build' as 'None'. The 'Requirements List' includes details about reagent transfer (290 µL of reagent), STD/QC, and study samples. The 'Risk Assessment' is blank, and the 'Testing Plan' is also blank. The 'Approved by' field is filled with 'CELERION\zomam01 (04 Mar 2019 08:07:04) Zoma, Maria'.
- Middle Screenshot (Development and Testing):** Shows a 'Request Type' of 'Change Request' and 'Current Build' as '2'. The 'Requirements List' details sample dilution in human serum and labware. The 'Risk Assessment' is 'Low Risk'. The 'Testing Plan' describes qualification of dilution steps. The 'Approved by' field is filled with 'CELERION\schibr01 (03 Sep 2019 12:49:29) Schibi, Rebeca'.
- Right Screenshot (Release):** Shows a 'Request Type' of 'Change Request' and 'Current Build' as '3'. The 'Requirements List' details 'User Output' dialogues and warnings. The 'Risk Assessment' is 'Low Risk'. The 'Testing Plan' describes simulation runs. The 'Approved by' field is filled with 'celeron\matthb01 (07 Apr 2020 09:43:58) MATTHEI, Bernd'.

Request for a new method to be approved by TFM: no/samples, timeframe etc.

Approval and Release Implementation in SOP Validation Productive usage

Liquid Handling and Error Recognition

Total Aspiration and Dispense Monitoring on HAMILTON Microlab® STARline

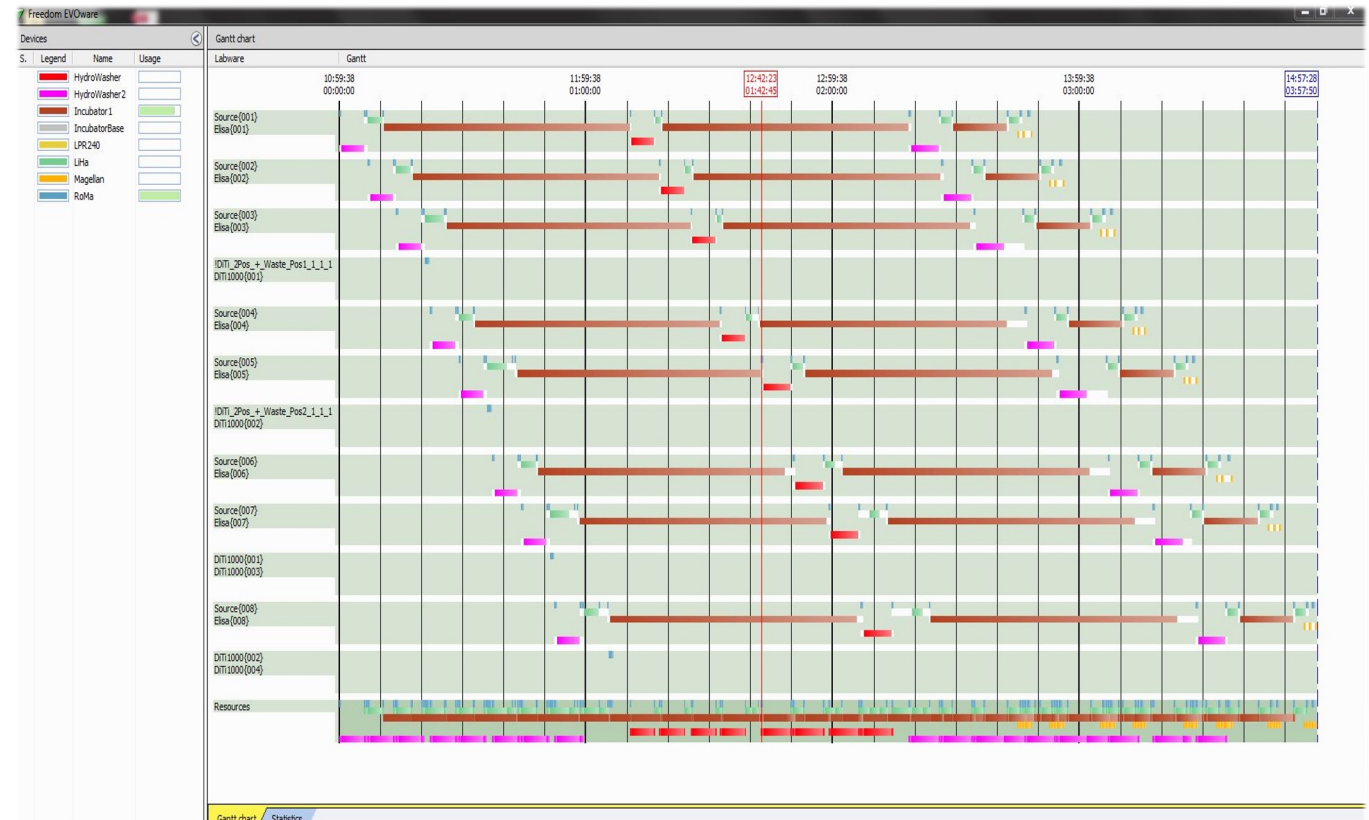


Left: Recording and monitoring of complete pressure curve during aspiration and dispense

Right: User defined tolerance bands (green and red): If measured value leaves the tolerance band, pipetting stops immediately and error handling is executed. Requires recording of pressure curves for each liquid class and volume

Working With Schedulers

Staggered Plate Handling on the Tecan Freedom® EVO



A Scheduler allows to handle multiple plates and resources at the same time. While one plate is on a washer, another plate gets pipetted on the deck, while the gripper already replaces empty tip boxes

Schedulers allow for higher throughput, keep incubation times constant and transfer the assay from a linear to a multi-dimensional process.

Consider to have back-up and recovery processes.

Unique Applications

Preparation of Calibrators and quality control samples on the Tecan Freedom® EVO

Labnotes: Definition and Documentation of Spiking Scheme

Spiking Scheme								
Final Solution			Spike Solution			Diluent		
Name	Concentration	Volume (mL)	Name	Concentration	Volume (mL)	Name(s)	Volume (mL)	
	ng/mL			ng/mL				
1.	DQC	495500	0.1800	WS1 QC	495500	0.1800	monkey plasma pool	0.0000
2.	ULOQ	10000	0.0000	WS3 QC	10000.0	0.0000	monkey plasma pool	0.0000
3.	HQC	7500	0.5000	WS3 QC	10000.0	0.3750	monkey plasma pool	0.1250
4.	MQC	900.0	0.5000	WS4 QC	1000.00	0.4500	monkey plasma pool	0.0500
5.	LQC	150.0	0.5000	WS4 QC	1000.00	0.0750	monkey plasma pool	0.4250
6.	LLOQ	50.00	0.5000	WS5 QC	100.000	0.2500	monkey plasma pool	0.2500
7.						0.0000		0.0000

Transfer



Spiking Robot: Execution of Spiking Scheme

	Final Solution ID	Final Solution Concentration (ug/ml)	Spiking SolutionID	Spiking Solution Concentration (ug/ml)	Final Volume according to Method (ml)	Solvent volume (ml)	Source volume (ml)
1	DQC	495500.0	WS1 QC	495500.0	0.5	0.0	0.5
2	ULOQ	10000.0	WS3 QC	10000.0	0.5	0.0	0.5
3	HQC	7500.0	WS3 QC	10000.0	0.5	0.125	0.375
4	MQC	900.0	WS4 QC	1000.0	0.5	0.05	0.45
5	LQC	150.0	WS4 QC	1000.0	0.5	0.425	0.075
6	LLQC	50.0	WS5 QC	100.0	0.5	0.25	0.25

Documentation

Execution

Spiking scheme transferred from Labnotes into a custom program, listing source and destination concentrations, with autonomous calculation of volumes and choice of appropriate tip size for the specific transfer volume

Still the Biggest Challenge..... and How to Overcome it

Standards and QCs labelled on Samplitag (Samplision), driven from ELN



Plates labelled with Print vario (Analytik Jena) with Run ID and ELN ID

Barcode verification on Hamilton Star Worklist driven from ELN

Inadequate labels on tubes sent from central labs: limitation of traceability, relabeling often necessary



No «white space» for start/end of barcode

Horizontally affixed label – not readable (even not with handheld scanners)

!! Different labware used for study samples may lead to false determination of filling status !!
Request tester «kit» (readily labelled sample tube) from central lab/clinic

A few facts

- ✓ Throughput increase (Especially seen in new lab technicians):
 - 1 FTA runs 8 plates on robots vs 3-4 plates manually: 200-267%
 - 1 FTA can start 2 series/8 plates sequentially (assay dependent), when readout is performed overnight: 400-532%

- ✓ Walk-away time for other tasks:
 - “Free time” during manual assay (assay dependent): approx. 1h (since time is used for prep of reagents during incubation steps etc.)
 - Walk-away time in a 8 plate series: approx. 3h, being effectively used for sample sorting for next series, run planning, result evaluation

- ✓ Assay robustness and reproducibility
 - Run success rate (assay dependent) at between 94-98% for robotic runs
 - Incurred sample reproducibility (assay dependent) between 96-98% for robotic runs

Summary – Automation Capabilities

- ✓ 21 CFR Part 11 compliant systems, interaction with LIMS, and ELN (paperless)
- ✓ All robotic processes worklist driven with barcode comparison and error recognition/reporting
- ✓

Designated robotic platforms for all laboratory areas and methodologies including

- Preparation of working solutions, calibrators and quality control samples
- Sample transfer from tube to plate incl. dilutions
- Radioimmunoassay applications
- Immunoassay systems with ELISA, Alpha-Lisa, Fluorescence and ECL readout
- Solid-phase extraction for LC-MS/MS
- Sample prep for Flow Cytometry (whole blood samples)

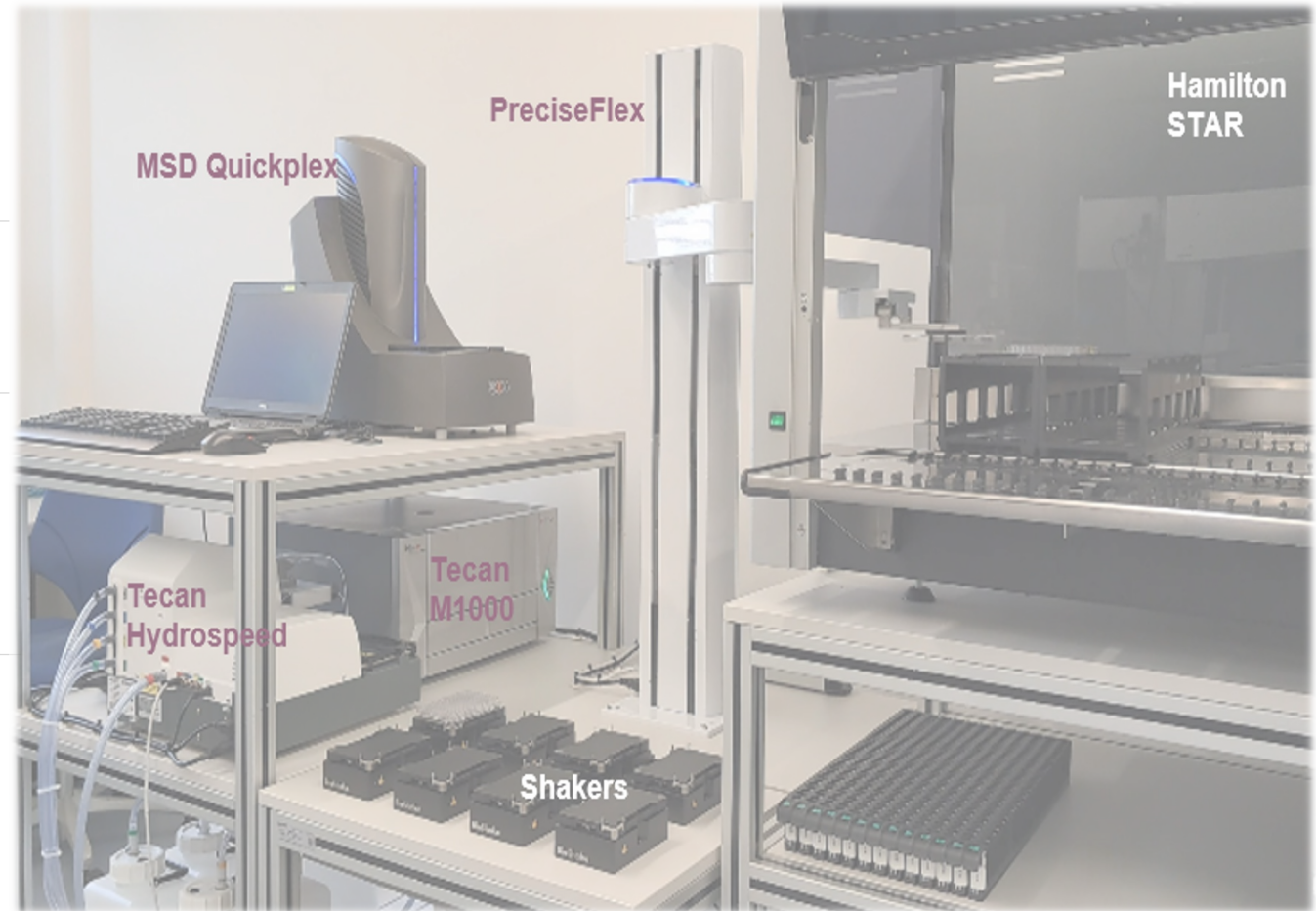


Further Literature available on our website

- ✓ Introducing automation to a regulated laboratory – an experience report
Bioanalysis (2020) 12(10), 643-647

- ✓ A Fully Automated Workstation for SPE Applications **Celerion White Paper** (2019)

- ✓ A Liquid Handling Robot for Robust and Reproducible Preparation of Standard and Quality Control
Adv Robot Autom (2017) 6:1, 1-5



Acknowledgements:

- Rebeca Schibli
- Elisabeth Friedhoff
- Larisa Anzel

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