

## 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  $\rightarrow$  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) Pri		Attachments (5)	Tecan Freedom EVO PQ Celerion - FZRH SOP.40015-01 Tecan EVO PQ (Version 12)	Celerion Translating Express to
Equipment Recurring Task Celerion - FZRHSOP-13002-01 Equipment Recurring Task (Version 02)  ID: EQ-ZRH-RLH-1069 / PM 20 - 001 *Performed D	Equipment Non-Recurring Task Celerion - FZRHSOP.13002-02 Equipment Non-Recurring Task (Version 02)		PQ ID: *Performed Date: 29 Jul 2020 III *PQ: Start Up / Shut Down / D	EQ-ZRH-RLH-1069 / PQ 20 - 020          New       Equipment ID:       EQ-ZRH-RLH-1069         Daily Maintenance as per SOP Performed
Check Tasks Performed	ID:       EQ-ZRH-RLH-1069 / Out of Service 20 - 003         *Task:       Equipment was put out of service         Equipment was put out of service       Image: Control of Service Date:         Details       *Cout of Service Date:         *Reason:       Image: Control of the service made of the service mad		*Microtiter Plate:       Costar Assey Plate 9         *No. of Wells Aliquoted:	98 Well (9018) CKS/ZRH/18 - 00835
*Task Pass / Fail Status:       *Task Pass / Fail Status:         *Results Details:       *Results Details:         write down results obtained or refer to supporting documentation (e.g. OD values, service report, calibration certificate, etc.)       See attached service report         *SoftMax Results printed into .pdf file:       N/AP       pdf need to be created before algoing "Compiled by"	A series of 3 consection (serial and with strong tape wherever necessary (e.g A series of 3 consecutive full capacity run production again (lonfiles/Macro-files of a *Location of Supporting Documentation: Electronic copy saved	Isst connection, another abort. Solution: all cable connection (serial and USB COM) at devices and computer rep with strong tape wherever necessary (e.g. LPR240). A series of 3 consecutive full capacity runs (water) will be performed to ensure sy: oroduction again (loofiles/Macro-files of aborted runs and successful runs attache in of Supporting Documentation: Electronic copy saved in server. No printouts available.		08.9         Pass         101.5         Pass         * Accuracy (%): Between 98.0% - 102.0%         * Precision (CV %): Less or equal to 2.0%         Pass         Pass
*Location of Supporting Documentation: Electronic copy saved in server. No printouts available.  Equipment Status Following Recurring Task(s) needs to be Performed: PQ A Nearest date among the service in the service	Equipment Tagged "Out of Service": Yes	*Approx. Out of Service Time: *Compiled by: CELERION\groesm01 (06 Aug 202	and Correctness by: CELERION\schibr01 (30 Jul Add Comment	Il 2020 09:08:40) Schibli, Rebeca
Add Comment	Add Comment	*Reviewed for Completeness and Co CELERION\gabela01 (06 Aug 2020	Assessment 1 Action: Comments: Approved by (System Owner):	for Failed Qualification Tasks

## Routine Checks With Associated Documentation in the ELN Labnotes

			EQ-Z	RH-RLH-10	69 / PC	20 - 021		
Performed Date:	07 Aug 2020	<u>W</u>	*PQ: New	:	•	Equipment ID:	EQ-ZRH-F	RLH-1069
	Start U	p / Shut	Down / Daily I	laintenanc	e as pe	r SOP Perfo	rmed	
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*No. of Wells Aliquoted:				48				
Test Solution: 0.0025 % Methyl O			Methyl Orange S	olutions RSP/Z	2RH/20 -	008458/ZRHSC	P.40009_v03	
Balance:								
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#### **Development of Automated Methods, Testing and Release**

Request for a new method to be

approved by TFM:

no/samples, timeframe etc.

			Attac		Attachmenta (10) Print	Audit Log Print	
Liquid Handling	Robotic Methods Change Control ( New / Up 13 Least Resting Industri Method Charge Cardial (Traven K2)	Liquid Handling F Celeros - 7291807-2011-85	Robotic Methods Change Control ( New / Updates ) Liquid Handling Robotic Method Change Control (Version M)	Liquid Handling	Robotic Methods Change Control ( New / Updates )	anion	-
ID:	SM3-445 / LHR Method CC	ID:	SM3-445 / LHR Method CC - Release	ID:	SM3-445 / LHR Method CC - Released Build 3		
Computer and System	S210 CS218 Hamilton STAR 8	Computerized Bystem CS	210 CS218 Hamilton STAR 8	Computerand System C	S210 CS218 Hamilton STAR 8		
	Requirements List (Request, Evaluation		Requirements List (Request, Evaluation and App		Requirements List (Request, Evaluation and Approval)		
•Request Type:	New E Current Bull	Pagest Turner	Channel Backet	"Remeat Type"	Change Browni III Manual Build: 2 manual and		
*Requirements:	<ul> <li>Transfer 290 pL of reagent (REA divent) to Nanc 0.45mL V-both</li> <li>Transfer 10 pL of STD, QC and study samples as per WL into th</li> </ul>	"Requirements:	Addition of the deck layout image in the user claicog. Currently, the decklayout	"Regultements:	Addition of "User Output" dialogs (popup windows) to guide the user to:		
(Detailed description of how the robotic method needs to partners)	<ul> <li>Only the first half of the Nunc plate to be used. One Nunc plate ( Tecan BVO.</li> <li>Tecan BVO.</li> </ul>	(Detailed description of how	hown when the user starts the method.	(Detailed description of hear	1. use the correct STD/QC carrier 2. correctly load carriers/labware on the autoload tray		
	- GC Init LQC, MQC, HQC - MRD to be centermed to all Nunc plates available, before sampli	the robotic method seeds to partorini	Following sample dilution in human serum are required: 1:10 ( 90 µL serum + 10 µL sample)	the robotic method needs to parliam)	3. verify that enough volume is available for both reagents and STD/QC		
	<ul> <li>Maximum number of analytical runs or assay plates: 8</li> <li>No empty wells are allowed. Wells not planned to have study sa</li> </ul>		1:20 (190 µL serum + 10 µL sample) 1:30 (290 µL serum + 10 µL sample)		Addition of warning when loading worklist -> user is reminded to sort the worklist and to add "serum" in posi applicable)	ion A1/A2 (#	
	<ul> <li>STD and GC tubes: Sarstedt Cat. No. 72694, 2mL</li> <li>Dilution plates: Nunc. 96-well, 0.45 mL Cat No. 249544</li> </ul>	L. L	Labware: Nunc 96-Well 0.45 mL and 50 µL/300 µL tips		Addition of user warnings (pop up windows) when dilutions other than 1:25 are specified in the worklist; user	r will be	
	- No additional diution in serum needed.		f capacity allows it, optional additional dilutions 1:50 (490 µL, serum + 10 µL, sample)		informed and method will be aborted before any liquid transfer. Since only the validated (CA22328) dilution applied, the diluent volume is no longer calculated based on the dilution factorisample volume, making a dilu-	/25 will be ant *volume	
			1:100 (990 µL serum + 10 µL sample) abware: DWP 96-Well 2:00 mL and 50 µL/1000 µL tips		amay" (list) unnecessary; diluent volume is now fix to 240 ul, (DF 25 = 240 ul, dilutent + 10 ul, sample).		
-Assessed by	CELEBION committe de Mar 2018 de 57 del Zoma Marita				Update the saving path of trace and output file so that Trace and Output File can be found in S1CS200ICS2	12-Output Files	Approval and
							Approvarianu
** this section is to	be left empty for new methods **	*Compiled by:	CELERIONIschibr01 (03 Sep 2019 12:49:29) Schibli, Rebeca	"Compiled by:	CELERIONIachibr01 (07 Apr 2020 09:43:58) Schibil, Rebeca	P	Release
Risk:			and the set Cables	Disk Assessment	(Consolute all Calde)		Implementation i
POER Accecoment		Nisk Assessment (d	complete all Fields)	POSK Addensionent	(Complete all Helds)		SOP
Testing Plan		Risk Assassment		First Assessment	Low Fox		JOF
			This is an additional request that will be guaranted before proceeding with the the quarantee status of any steps needsed in build 1. Wethod SQP may need to be updated to described the additional steps and g	TOTA APPPENDEN.	Changes in the script do not affect any liquid transfer or any assay parameters. No sample analysis performed yet using the automated procedure.		<ul> <li>Validation</li> <li>Draductive users</li> </ul>
Approved by:	[	Testing Plan:	Qualification of the dilution steps will include liquid class testing, water run an amplies.	Teeting Plan:	Simulation run wil maximum number of worklist -> Verification of trace and output file location. Simulation nu wil 1 worklist but aborted -> Verification of trace and output file location Simulation nu wil worklist contraining dilution factor other than 1.25 Review by a second programmer.		FIGULCIVE USAG
•Self Texts:	Development and Testing Accuracy with gravimetrics: association 10 all security of LLD +1 mm, local tribuctor and d	Approved by:	CELERION/wuttkr01 (03 Sep 2019 13:25:02) Wuttke, René	Approved by:	celerice/matthb01 (07 Apr 2020 14:41:54) MATTHE 5, Bernd	-	
simulation runs, processon and/o accuracy toxin, dead columns, determined toxin, dead	If aspiration 290 pL reagent w/ cLLD, -2 mm, liquid following and Precision with optorimetrics;						
name with load materials etc.	10 µL methylorange on 250 µL water, and mix (48 points) = or		Development and Testing		Development and Testing		
-Run-Through Test:	06Mar2019 Water rune CA12345-T1 to TE: CA12345_T1-T8_	"Self Tests: Document reference to e.g.	Precision 90 µL, 190 µL, and 290 µL serum see attachments: Celerion_SM3_445_v1_0_StandardVolume_Serum_DispenseSurface_E/	*Self Teeta: Document reference to e.g.	See attachments for runs CA12345_R1 to R11. Results of the simulation runs were as expected.		
ner with lost materials semulater an actual analytical net., e.g.	18 Cuspatrie 06-03-2019 10-34-25 csv . Expected pretting in the output file. Bancodes of samples and MRD plate read an to 6 times as initially tested.	scrucation runs, precision and/or accuracy lesits, dead volumes determination, gravimetric lesit,	Celerion SM3 445 v1 0 StandardVolume Serum DispenseSurface El Celerion SM3 445 v1 0 StandardVolume Serum DispenseSurface El	scrutation runs, precision and accuracy tests, dead volumes			
		runs with load materials etc.	Accuracy 90 µL to 290 µL of serum see attachment. See attachment x_StandardVolume_Serum_DispenseSurface_Empty_M	runs with lost materials etc.			
Decarrent reference to eaceed	RDCA22328_R47: RDCA22328_R47_OutputFile_13-03-2019	"Run-Through Test:	Water run: CA12345_T1_TraceFile_17-09-2019_11-42-39.tro / CA12345_	"Run-Through Test	NAP.		
	STD 2 reported "pipetting error" and it was added manually. C Stress test	Document reference to a success run with lest materials simulating an actual analytical run, e.s.	Max. capacity for 1:100 dilution on simulation: CA12345_T2-TP_TraceFile Max. capacity for 1:30 dilution on simulation: CA12345_T10-T17_TraceFile	Discament reference to a succe run with test materials simulat	antel reg		
*Additional Information	E NOP	trace/subult file.		trace/output like.			
		*P&A and Stress Test:	Dilutions 1:10, 1:25, 1:100 tested in RDCA22328_R92/R93.	P&A and Stress Test	IN AP		
Proprietation and Inc.	CELEBON AND STOLEN AND STOLEN AND STOLEN AND STOLEN	run, e.g. run ID	RDCA22328_R92-R93_TraceFile_01-11-2019_11-41-46.tro	Decanent reference to eaces ran, e.g. ran ID	shaft		
"Reviewed/Tested by:	CELERION comamol (28 Mar 2019 13:12 64) Zoma, Marila			a conservation of			
	Release	*Additional Information:	Dilution 1:20, 1:30, and 1:50 can be used as initially requested, but were in Dilution bellow 1:10 or higher than 1:100 cannot be performed by the robo	*Additional Information	Test nun CA26656-01_E11 met criteria (ind. STDs. QCs. DQCs)		
•Released Date:	21 Mar 2019		MRD mixing volume increased to 50 µL instead of 40 µL and mixing heigh hotiom of the well. These chances solved the high CV observed during val				
"Approved by (RnD):	E CELERIOWarennp01 (28 Mar 2019 13:80:03) Brenneck	*Programmed by:	CELERION/schibr01 (05 Nov 2019 09:35:54) Schibli, Rebeca	"Programmed by:	CELERIONachibr01 (07 Apr 2020 16:52:54) Schibil, Rebece	4	
		"Reviewed/Tested by:	CELERIONaelges01 (05 Nov 2019 09:39:38) ZELGER, Sabine	-Reviewed/Tested by:	CELERIONgabela01 (05 Apr 2020 05:54:25) Gabel, Anke	*	
elarification: field "Com without any impact in th	<ul> <li>reputerized System and LHR Type" is a non-editable, linked fee he data opileoted. Field is for information purposes.</li> </ul>						
27 Mar 2018 12:67 (UTC	+1) (CELERION wohlbr01):		Release		Release		
Accept Exception : Con	nputarized Bystem and LHR Type, Required field incomplete	"Released Date:	06 Nov 2019 🔘	"Released Date:	17 Apr 2020 V Released Build:	3	
		*Approved by (SDIPI):	E CELERION wutthr01 (06 Nov 2019 12:51:57) Wutthe, René	"Approved by (SDIPI):	celerionimatthb01 (17 Apr 2020 14:02:23) MATTHE 5, Bernd	1	
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### **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 <u>each liquid class and volume</u>



### **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



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

No «white space» for start/end of barcode

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

necessary

Horizontally affixed label - not readable (even not with handhold scanners)



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

Barcode verification on Hamilton Star Worklist driven from ELN

!! 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

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



### 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
  - 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:

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