Commentary

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Introducing automation to a regulated laboratory – an experience report

Michael Gröschl*,[1]

[1]Celerion Switzerland AG, Allmendstrasse 32, Fehraltorf 8320, Switzerland

*Author for correspondence: michael.groeschl@celerion.com

First draft submitted: 28 April 2020; Accepted for publication: 12 May 2020; Published online: 5 June 2020

Keywords: 21CFRp11 • computerized system validation • laboratory automation • liquid handling

The classic operation areas for laboratory automation are clinical routine and central laboratories. The necessity to perform repetitive analysis 24/7 and the cost pressures in this area were reasons to introduce automation methods decades ago. In other laboratory areas with less repetitive work, the relationship with automation was more distant. The effort to invest in automation was often not met with the expected benefits. However, with increasing demands on throughput as well as traceability and reproducibility, automation has increasingly found a way into GxP-regulated laboratories. I want to report the advantages and difficulties in transforming our laboratories in the automated direction and promote a better acceptance for this indispensable support for our daily work.

What do you want to achieve?

When the decision is made to automate work, different people in your organization may have different expectations about the end results. Some may focus on the increased throughput, which is a strong argument to get the funding approved by upper management. In fact, robots can work 24/7, which is however rarely ever required. Nevertheless, in our facility, it is standard to run the last robot run of the day overnight, utilizing assay time when the last laboratory technician has already left. Moreover, a typical standard ELISA robot with integrated plate washers and a reader allows the increase of throughput tenfold, with just one laboratory technician required to feed the system with samples and reagents. This increase is lower in other laboratory areas, such as RIA or LC–MS, with the counters or mass spectrometers being the back end bottleneck.

Still, while robots conduct the assay, human resources are free for other tasks, for example, compiling the documentation, planning new runs or evaluating already performed ones. These tasks would require additional time or resources, if the technician is permanently engaged in the laboratory for manual sample workup.

From the technical point of view, the uncontested increase in assay robustness and reproducibility additionally support the throughput aspect, with less runs failing due to human workup errors and less variability observed between results created by one robot compared with multiple manually prepared data. This is extremely beneficial not only for PK profiles and very stable ADA control values over a study, but also to yield strong reproducibility of yet analyzed samples, namely during incurred sample reproducibility runs.

Finally, the focus on data traceability became decisive to proceed with automated systems. All state-of-the-art robot software from notable vendors provide the features to support the requirements of CFR21 part 11 [1] or the EMA [2]. It is imperative that the software recognizes whether the login belongs to an administrator (full access rights) or to an end user (limited rights only). This takes away the fear from laboratory technicians that they could choose something wrong or make accidental changes.

Log files written by the software allow to trace back any activity executed by the system. In contrast to manual work, this allows for full traceability of all actions at any time, and helps to investigate, if unexpected results occur. In advanced robotic software types, there shall be a possibility to retrieve the most important information of these log files in a reader friendly and condensed format, especially to provide lists with reported liquid transfer errors.

Other features, such as audit trails and electronic signatures are most beneficial in the regulated environment, since this easily allows tracing back which programmer made changes and for what reason.

newlands press

These are all valuable advantages and since modern robot platforms and softwares are capable of providing them all, there is the good chance that your laboratory will benefit from some or all of these advantages.

Selecting the right systems

The choice of the right robotic system(s) is decisive for it's success and acceptance within your company. This requires a clear presetting of which areas in the laboratory you want to automate. The more standardized the application is, the easier you will find the automated solution.

For example, an ELISA workstation with worklist-driven sample transfer from tube to 96-well plate, including wash cycles, reagent addition and incubation, resulting in a final reader output, is relatively easy to handle and practically all major vendors can provide fit-for-purpose solutions with their own peripheral equipment being easily integrated in their robots.

But how about special requirements like SPE in LC–MS, using either vacuum or positive pressure units incorporated in the liquid handler? For such requirements, the integration group of the vendor will definitely be challenged when it comes to space requirements for the third-party equipment (e.g., positive pressure units or centrifuges) and the stable integration of the driver software and other programs into the robot software. The recommendation is to get in touch with the potential vendors to find out about their capabilities, their accessibility to third-party device drivers and their experience on integrating those into their robots.

If possible, get in contact with previous customers of integration projects. An experience report from these customers is certainly more meaningful than any promise made by a sales representative. Also, ask for experiences with the skills and availability of service technicians.

Consideration of the support of your system hardware and the programmed application in the future is also important, for example:

- Software and firmware updates;
- Changes in IT components or operating system;
- Availability of disposable parts;
- Can the vendor still support the application, if the programmer has left the company or retired?

If an application is not fully based on 'off-the-shelf' programming, requiring further, customized plug-ins, request the source code of the plug-ins to ensure that you can access the application, even when the vendor is not able to support it any further.

With regard to the flexibility and complexity of robotic systems, our facility made good experience not to design a platform to cover the entire workload of the assays. Since many assays require a defined interruption, such as over-night incubation, we tend to split the assay between platforms at exactly these interruption points. While one platform is dedicated to run the worklist-driven tube-to-plate transfer, other platforms are specialized in plate processing (either ELISA workup or SPE processing). This has three big advantages:

- The platforms can be smaller, only covering the intended usage (which makes it cheaper too);
- The platforms are not occupied during the complete assay procedure and the next set of runs can be started, while the plates get further processed on the second robot;
- If one platform is out of order, these assay steps can be recovered by manual processing, while the remaining parts of the assay can still be processed on the unaffected platform.

Take time & care for your user requirements

It is mandatory to clearly define up-front, what you expect from the system when being in routine service, and to consider further possible applications. Application engineers from various vendors told me, the worst scenario occurs, if a customer does not clearly specify the application and the requirements. In this case, the automation project will hardly succeed, as the customer will receive a system not fully fit for the intended use. Consequently, the laboratory personnel may develop resentments against the robots, not seeing the potentials, but only the errors and immaturities. Frustration is unavoidable, and another expensive device will decay in the material warehouse until being depreciated for tax purposes.

To meet all the user requirements, the validation team should consist of end users and subject matter experts, IT (for the connection to the company network) and QA (for regulatory requirements for the software). The implementation of laboratory automation must be a team approach, in order to succeed.

Validation: when & how far

If the selection for the system has been made based on technical, compliance and economical considerations, the users need to decide, what validation efforts are necessary to bring the system into a productive setting.

A Pharma company, focused on one or two applications, can combine the validation of the robotic system (with software safety, data flow and any other general aspects covered by the working group information technology (AGIT) guidelines [3–5]) in combination with the purely method specific validation aspects, such as testing and release of specific liquid classes, labware and dilution factors.

In the case of a CRO, one method will rarely run for more 1–3 months before the system is switched to another project. Consequently, the CRO will separate the system-related validation parts from the bioanalytical topics, since the vast variability of methods will require partial robot validation for any new bioanalytical method.

It is recommended to standardize as much of the repetitive parts of the programming as possible (e.g., worklist readout and compilation of output files) to keep these constant between methods. This makes validation much easier and the system more user friendly. It is also recommended to include induced errors to the validation of the system (and later to the method) to ensure, that process recovery, error handling and error reporting are set properly.

Monitoring the system performance

Reliability of the data is based on the continuous monitoring of the robotic system. To ensure that the system performs as expected, a set of quick and easy performance checks should be set up. These shall cover at a minimum the test of the liquid-handling system (accuracy and precision testing, system tightness checks) and any incorporated devices (e.g., plate washers or readers). You may apply the same tests as executed for the stand-alone equipment in the laboratory (e.g., handhold pipettes) and apply the same acceptance criteria. The latter simply helps not to get in argumentation trouble during audits, if different criteria for manual equipment versus robotic systems are applied. In general, tests performed by qualified service providers during the regular preventive maintenance should have stricter criteria, but consider that you want to check your system on more frequent basis. Some vendors provide predefined programs for performance testing of the liquid handler or even provide test routines for the peripheral equipment (e.g., optical checks of the readers with specific test plates). Nevertheless, develop your own internal test to have a second perspective on the system. A preconfigured test for the tightness of the pipetting channels tells you a lot about the functionality of the hardware, but not whether a specific volatile solvent can be retained in the pipette tip when the channels are moving over the deck. An experience-based assessment of possible mistakes is necessary to avoid unpleasant surprises such as dripping, which may lead to contamination issues.

One extremely helpful feature provided by some vendors allows monitoring the pressure curve of a liquid inside the tip during aspiration and dispensing. The user needs to invest time to 'train' the software on how the different typical assay volumes behave. Stored in the appropriate liquid class databases, the software will later clearly differentiate whether a volume was properly transferred or not. This reporting can be combined with predefined error handling, which for example excludes the affected sample or retries with a fresh tip. Of course, all these activities will be documented in a report file.

Challenges & how to overcome them

Of course, where there is light there are also shadows. A lot of persuasion had to be done to increase acceptance for automated liquid handlers. Still, there are many daily problems that make extensive use of the robots difficult.

First, there is the problem of inadequate barcode labeling of the sample tubes. Hand-held scanners can be directed by the user to catch the barcode on the cryovial, regardless whether it is affixed straight or crooked. Integrated scanners require the barcode within little tolerance at a certain height, specific angle and at a high resolution quality. If these conditions are met, the barcode reading as a basis of worklist-driven robotic processes, will be ideal. But when the barcodes are affixed in a mess, the loading part of the run will be an uphill task. To overcome these problems, we generally provide the clinics with instructions and specification for the labels and additionally request a tester with an affixed label before the first sample is drawn. This allows us to intervene if necessary and we also see increased quality in the sample labeling in the shipments to our site.

One main prerequisite for using liquid handling robots is the availability of a sample tubes with sufficient filling volumes. While the laboratory technician in a manual assay can visually inspect the tube and work with practically no surplus volume during aspiration, the robot needs a certain surplus volume to detect and aspirate the assay volume. Unfortunately, there is no simple rule of thumb on how large this volume should be. It depends on the

shape and dimensions of the tube (v-shape < round bottom < flat bottom), the professional measurement of the tubes, as well as the chosen liquid class (immersion depth, aspiration speed). Different cryotubes used in the same robotic method do not allow for perfect tube definition and consequently lead to unnecessary errors in liquid level detection/volume calculation. It is recommended, to keep control for the other consumables (as assay plates) too, since like for like is not always the case, as minimal differences in the dimensions may have dramatic impact on the assay performance.

In an optimal scenario, the sample tubes in the study are all the same catalog number and the filling status corresponds with the predefined volume of the clinical manifest. In the worst-case scenario, samples get delivered in very different tubes (this happens especially in late stage clinical trials), or the samples have been split in aliquots with none of these containing the required volume. Communication and training of the clinical personnel are the only ways to overcome this common and challenging issue, otherwise you may consider to bulk different aliquots together to achieve the required volume at least in a single tube.

Sample quality also affects robotic liquid handlers more than manual pipettors. If there are clots or smears, the laboratory technician on the bench can react by removing the clot, remixing the remaining volume and transferring the required volume with a fresh pipette tip. A clot on a robot with the super thin outlet of the special tips will definitely cause an aspiration error (which should be handled via 'discard tip and retry with new tip'), but the error may reoccur and the sample may finally not be pipetted. Even when properly documented in the output file, the sample must be reassayed, with corresponding impact on material costs and timelines. A recommendation from our experience: all samples should be vortexed and subsequently centrifuged before loading them into the robot sample carriers. This ensures all sample adhesions in the cap are spinned into the vial and the clot hopefully gets squeezed at the bottom of the cryotube. This should reduce clot errors to a minimum.

One challenge that we are often facing during development and qualification of new robotic methods is the availability of reference substances and critical reagents in sufficient amounts. It must be clear that robotic methods require larger volumes (as described above for the sample volumes) and the surplus volume after one run is lost (do not keep it and add the reagents for the next run on top in the troughs on the robot deck). A rough estimation is to spend 8% more volume of critical reagents during sample analysis compared with purely manual runs. For method development and qualification, the ratio may be even bigger.

We try to keep material consumption to a minimum, starting with all tests with dummy plates and water runs, transferring the method to expired materials before doing the final test with true reagents. But customers (external sponsors and internal study directors) need to understand that a certain increase in material costs is unavoidable. However, this will be balanced in the long run by increased assay robustness and reduced number of reassays.

Build a core team

The success of the introduction of robots depends on the personnel who are responsible for the special tasks (programming, maintenance, troubleshooting) and their daily use and efficiency. Employees who are skeptical about the machines and consider them 'competitors' will find it difficult to become enthusiastic users.

It is therefore advisable to select the technically minded colleagues from the existing workforce, and to introduce them to the robots with intensive practical training. Consequently, form core teams that can then work independently and reliably with the robots. It is important that these trained employees regularly carry out suitable 'dummy runs' at times when the robots are not used for studies for various reasons, in order to remain active.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. US FDA. FDA 21 CFR Part 11, Code of Federal Regulations (1997). https://www.fda.gov/media/75414/download
2. US FDA. EU Guidelines to GMP Annex 11 Computerized Systems (2011). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf
3. EU Directorate for the Quality of Medicines and Healthcare. Guidelines for the Validation of Computerized Systems (2018). https://www.edqm.eu/sites/default/files/guidelines-omcl-computerised_systems-core_document-march2018.pdf
4. *Pharmaceutical Computer Systems Validation: Quality Assurance, Risk Management and Regulatory Compliance, Informa Healthcare (2nd Edition)*. Wingate G (Ed.). London, UK (2010).
5. International Society for Pharmaceutical Engineering. GAMP Good Practice Guide: Validation of Laboratory Computerized Systems ISPE (2005). https://ispe.org/publications/guidance-documents/gamp-good-practice-guide-gxp-compliant-laboratory-computerized-systems