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Whitepaper

Robotics & automation on the brink of transforming pharma QC

Projects underway to boost the reliability, data integrity and productivity of microbiological testing

The ongoing coronavirus pandemic has highlighted the need to speed up getting therapeutics and vaccines to the market. Massive investments are leading to progress at all stages, from lead discovery and optimization to clinical trials, and further along the value chain in manufacturing and quality control (QC). In QC, there is still huge potential to accelerate the release of safe products. Committed to staying one step ahead of customer expectations, we at MilliporeSigma are partnering with companies in the pharmaceutical industry to automate the processes involved in microbiological QC testing. This approach to reduce human intervention by introducing robotic arms and/or stand-alone automated hardware into workflows, flanked by enhanced lab digitalization, carries the additional potential of lowering costs and minimizing the risk posed by human errors. To support the customer-focused development and refinement of its robotics and automation solutions, we are inviting QC professionals to join our User Advisory Group.

The transformation from operator-based to fully automated QC

Today, QC samples are taken at various points of the manufacturing process, from selecting the raw materials to examining the finished product. The samples are brought to the lab where they are processed by lab technicians who run a variety of tests using many different supplies. Along with the physical samples and the testing comes a large amount of data to process, including sample IDs, operator names, lot numbers of supplies, and of course test results. Lab data is very often still managed manually. In a survey we recently conducted, 62% of respondents replied they were still using paper or spreadsheets.

In fact, the whole QC process remains predominantly manual. This leaves room for errors, not because lab technicians are poorly trained or negligent, but because this is in the nature of human beings. A handling error can go unnoticed, making the investigations in the wake of out-of-specification results difficult, and entire batches may have to go to waste.

However, these labor-intensive tasks can be optimized for productivity, reliability, and data integrity. In our survey, we asked our customers what their challenges and expectations were for QC. The respondents ranked the need for greater throughput and real-time product release near the top. In the long term, QC is expected to leave the lab floor and be distributed along the manufacturing process, with testing being automated and performed in real-time. Any deviations will be reported instantly, and corrective action taken without delay. While probes and sensor technologies for physico-chemical parameters like temperature or pH are already being used in manufacturing processes, there is as yet no real-time technology to detect biocontaminants.

Robotic arms and stand-alone automated hardware

Our strategy for automation is to create standardized solutions. It is based on robotic arms and automated hardware, both of which reduce human intervention. In principle, a robotic arm replaces a human arm. It can be built with several articulations, rotation axes, and a specific tool at the end of the arm, typically a gripper that can grasp and manipulate objects. They all act together to perform a sequence of motions—one of potentially millions that can be programmed. Robotic arms are versatile, very precise, and the operations can be standardized and repeated in exactly the same way. Multiple operations can be run in parallel, for example by having the robotic arm grasp a sample while the previous one gets tested.

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Stand-alone automated modules, on the other hand, are stations with dedicated automatisms, much like pipetting robots. These stations are designed to execute a specific sequence of actions and are dedicated to a very specific step in the workflow, like opening a cover or sticking a label on a vial.

To automate a QC workflow, it needs to be reviewed and analyzed as a whole to determine which steps are better addressed by a robotic arm, and which by stand-alone automated components. Other steps can remain manual if efficiency, throughput, and financial considerations suggest this is better. All elements need to be integrated, meaning physically brought together and programmed to operate in conjunction with one another. The outcome can be a machine in a dedicated cabinet with multiple compartments and installed in a lab, or a mobile robot that can be used at multiple locations.

In step with GMP and GLP

In the pharmaceutical industry, automation solutions are designed to operate either in a lab, an isolator, a restricted-access barrier system (RABS) or a cleanroom, so good manufacturing practices (GMP) and good laboratory practices (GLP) have to be followed. Automated solutions must be compatible with aseptic techniques, not interfere with the production or testing, and not cause cross-contamination. There are many potential pitfalls, so the automation provider must be well-acquainted with QC applications or be guided by expertise when the automation components are devised and integrated. For example, robotic arms create turbulence as they move, so they must be positioned in a way that they do not interfere with the airflow or compromise the asepsis of the test. Above an open funnel or media plate there must be no movement at all. To enable cleaning and disinfection, the machines and devices have to be designed with smooth edges, and without nooks and crevices.

Digitalization as an enabler and an enhancer

When the workflow of a QC test is automated, so too is the management of the captured data. This is achieved by digitalization, which helps to optimize a number of other activities, such as test planning and stock management. To guarantee its integrity and traceability, the data is recorded digitally at each step of the workflow, from the selection of materials to sample collection, testing, incubation, and storage of the results.

Digitalization can also enhance data analytics by making it easier to track trends, prevent deviation, and facilitate investigations. Digitalizing the QC lab paves the way for a variety of tools and technologies, including laboratory information management systems (LIMS), electronic lab notebooks (ELNs), connected instruments, augmented reality glasses, voice control, smart labels, and block chain.

By enabling efficient and accurate data interaction between all elements, digitalization has a huge potential to improve lab efficiency. Implemented in combination with the automation of QC testing, the benefits are even greater.

Designing an automated bioburden testing solution

One of the several QC workflows we are exploring is the potential of robotics to automate bioburden testing (microbial limit testing) by purchasing a commercially available robotic arm and programming it to perform a test using the Milliflex Oasis® system. This revealed which steps of the workflow worked well and which needed optimization. The need became evident to adapt the existing bioburden testing equipment to make it more robot-friendly, and to create stand-alone modules with dedicated automatisms for very specific steps of the workflow. While many components used for bioburden testing were found to be suitable for automation, the entire work environment needed to be redevised.

Consumables: well suited as they are

When Milliflex Oasis® system was designed, our product engineers already had automation in mind, integrating preconfigured features for automation. The funnels and media plates are closed, making them compatible with spraying or fogging for decontamination. The funnel tray is easy for a robotic arm to load. The culture media plates can be stored at room temperature for up to a week, and the test procedure minimizes the risk of contamination thanks to contactless membrane-to-agar transfer. All these and other features make it easier to automate the process.

Traceability features were also integrated: the funnels and media plates are identified through a single ID, allowing them to be linked to each other, to the sample, and to the protocol followed and the materials used. The pump's drain tubing and check valves were designed to prevent cross contamination. Only a minimum of sanitation is required, and it is possible to fully integrate the pump. Thanks to these intrinsic features, Milliflex Oasis® system is probably the most suitable bioburden solution on the market for automation.

Hardware: adaptations needed

The pump itself was found to require adaptations for automation. We are redesigning it so it can be fully integrated into an automation environment. Some parts will become more prominent, others be placed under the work bench, and the pump will be piloted directly by the system controller. The aim is to design a standard automation version of the pump.

However, the pump is not the only piece of hardware being worked on. A few steps of the workflow will be optimized by integrating stand-alone automated components, including ones for handling samples and transferring liquids. Additional automated hardware for very specific tasks will complement the robotic arm. All these pieces of hardware are set to become standard items for all customer automation projects.

At this stage it is not possible to openly give more details on the automation components, but we are happy to share these under a non-disclosure agreement. QC professionals who would like to go even further are invited to share their opinion and test developed prototypes as part of our User Advisory Group.

The developed automation solution

The resulting automation solution is a cabinet comprising two areas: a class D storage area and an adjacent class C testing area. There is a robotic arm in each, and a hatch between the two areas for transferring material.

The storage area is loaded with all the consumables needed to run the tests: filtration funnels, media plates, rinse fluids, and other accessories. When entering the area, they are dusted in an air flow, and decontaminated by hydroxyperoxyde fogging in a dedicated tunnel. This good laboratory practice reduces the risk of cross-contamination. Samples enter this storage area with the same dusting and decontamination process. Each sample carries a label that a reader scans. The system knows all the test procedures for all sample types. It verifies that all the materials needed for the test are at hand and automatically groups the samples, so they can be tested in the order from the cleanest to the dirtiest.

The testing area is equipped with a robotic arm and dedicated stations with stand-alone automated hardware. One of these is an automation-adapted version of the Milliflex Oasis® pump. The robotic arm works on the different objects needed for testing, with the hardware operating simultaneously to optimize the throughput. All processes are managed by a system controller that is operated via a touchscreen located outside the cabinet.

The system records all critical steps to document that the test procedure has been performed as it should. Data related to materials, samples, and test execution, including the filtered volumes, are logged into a LIMS to ensure traceability.

Calculating the investment payback

To quantify the savings potential of QC automation, we developed a calculator tool to understand the total cost of ownership for customers. This meant breaking down all the costs involved in a QC workflow, including the direct costs of the work hours and materials needed for testing, but also indirect costs, including maintenance, training, and out-of-specification management. Also included are the one-off costs of implementing an automation solution, which helps to calculate the return on investment and reveal the savings by cost center.

A case study was performed for a generic bioburden workflow based on averaged real data from multiple sources. The calculator tool allowed to identify how automation reduced the total cost of ownership: labor was the biggest contributor to the cost savings, followed by out-of-specification investigations. The tool also allowed to calculate the payback and net present value of the automation investment. More details can be provided on demand.

We use this calculator tool to estimate the financial impact of automation projects when analyzing them with customers. Of course, the figures vary from one company to the next and depend on several parameters, for example the number of tests performed per year. In some cases, the return on investment may not be sufficient. In such cases, other ways of improving a QC workflow can be identified, such as implementing a traceability solution, digital assistance or semi-automation.

User feedback needed for optimization

The ultimate objective is a standardized integrated automated solution. As a leading worldwide supplier, our company will naturally provide the consumables, the adapted hardware pieces that deliver the application capabilities, and a full spectrum of dedicated services. But we intend to go one step further and act as a full partner to integrate all these components, including the robotics, housing, digital components, and the system controller interface. Some projects with customers in the pharmaceutical industry on several QC workflows are already underway.

We develop automation solutions for QC in an iterative process: after initially determining the requirements and specifications, a first prototype is designed, which is tested by real users. Their feedback is collected, the requirements and specifications changed where needed, and the prototype adapted accordingly. Typically, two to four such iteration cycles are needed to reach a design that becomes the standard.

To broaden our community of trial users, we are looking for QC professionals who are interested in joining our User Advisory Group to support the refinement of the developed automation solutions. This network offers participants the unique opportunity to bring in ideas and have their expectations and needs considered at the stage of product development. Anyone interested should contact us at automation@milliporesigma.com to discuss the details of such a collaboration.

Want to know more or join our User Advisory Group to support the development and refinement of QC automation solutions?

Send an email to: **automation@milliporesigma.com**

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

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