

Getting a handle on liquids: automation solutions for drug discovery

The accurate and precise measurement of liquids and the transport of exact volumes between vessels, or from one instrument to another, are processes that constitute the very essence of research. However, while this simple requirement for the meticulous handling of liquids has been ever-present in laboratories the world over, there has been dramatic evolution in the techniques and equipment used to perform such tasks, from the humble Pasteur pipette to today's automated liquid handling instruments. This article focuses on the latest developments in automated liquid handling for drug discovery, and the current trends that are shaping the industry, such as low-volume handling and miniaturisation, before looking ahead to the next steps that will lead to tomorrow's breakthroughs.

The need for high accuracy and high throughput in the search for new drug candidates has driven the development from manual methods towards automated liquid handling. Automation provides the throughput and consistency required to screen huge numbers of samples as rapidly as possible, leaving human hands free for less repetitive and more creative tasks, such as designing experiments and data analysis.

“Automated liquid handling addresses a multitude of high-throughput screening (HTS) challenges,” said Kevin Truempi, Product Manager of Automation Solutions at Agilent. “There is an ever-growing demand to screen and collect more data over multiple timepoints, vastly increasing the sample count for processing and analysis. Automated liquid handling systems are crucial for generating reproducible data at high throughput for improved downstream analysis.”

When implemented correctly, automation is

unsurpassable in terms of its ability to increase throughput capacity compared to what is possible by hand. By shortening screening time and improving the reliability and reproducibility of data, decisions can be made more quickly and with greater confidence, which can ultimately lead to significant cost savings. As Carola Schmidt, Global Director of Automated Solutions, Applied Genomics at PerkinElmer, explained: “Standardisation of drug discovery workflows by automating the liquid handling processes offers the highest return on investment in terms of the reduction of human error and accuracy improvement.”

The challenge for automated liquid handling in drug discovery is adapting to complex, physiologically-relevant assays. It is the systems that address this specific need that have the potential to deliver the most significant reductions in costs and timelines while enabling drug discovery companies to explore a much broader part of the available

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chemical space. “Libraries of millions of compounds in buffer solutions are required for screening. Utilising automation to prepare these samples quickly and accurately allows scientists to optimise their results, as well as their time,” said Harry Forsyth, Regional Sales Manager at Analytik Jena. This speeds up hit generation and hit-to-lead processes, which in turn increases the probability of generating promising clinical candidates.

The evolution of automation in drug discovery

Automation has been a part of drug discovery for decades, but recent years have seen major advances in liquid handling technologies. One notable trend has been that instrument manufacturers are continuously striving to achieve more with less, bringing about benefits in terms of affordability. Today, even laboratories with relatively small budgets can purchase equipment capable of performing tasks that were once the preserve of much larger and more expensive systems. “Systems are generally smaller in footprint and easier to use,” noted Joby Jenkins, Director of Product Strategy at SPT Labtech, “and as a result, companies of all sizes can reap the benefits of automation without the need for huge financial and infrastructure investments.”

This drive for optimisation has also led to the design of instruments with greater flexibility to suit a broader range of applications, ensuring a rapid return on investment. “The use of automated liquid handling systems now goes well beyond HTS,” commented Dr Rémi Magnan, Associate Director of Cellomics and Proteomics at Tecan. “Instruments are now providing solutions for compound management, assay development and ADME-Tox (Absorption, Distribution, Metabolism, Excretion and Toxicity) studies and immunogenicity screens.” Liquid handling solutions are also addressing the increasing number of cell-based assays, phenotypic screens and functional genomics/CRISPR screens to identify a better quality of hit from a physiologically-relevant test system.

Software is another area undergoing unprecedented change. Previously, engineers with specialist knowledge were required to program most of the earliest examples of automated liquid handling instruments. Today, instruments are equipped with intuitive, user-friendly interfaces, enabling laboratory personnel to carry out programming tasks, without the need for expertise in coding or robotics.

Factors to consider when implementing automated liquid handling

As the automation of liquid handling expands to cover every aspect of drug discovery, the range of available instrumentation is also growing, with systems to suit every application, laboratory space and budget. Identifying the right automated liquid handling instrument for a specific screening strategy can, therefore, feel like a daunting task. However, the process can be simplified by first considering three key factors, namely: reliability, media viscosity and software.

“The importance of reliability cannot be underestimated, not only of the instrument hardware itself, but also its fundamental dispensing mechanism. Both can be overlooked by end-users who are influenced by throughput, volume range, or price,” said Joby Jenkins at SPT Labtech. “Automated liquid handlers must deliver day-in, day-out and guarantee as much up time as possible. Furthermore, as volumes will inevitably decrease to reduce cost and increase throughput, the reliability of low-volume dispensing across a variety of liquid types becomes ever more critical to avoid compromising data integrity.”

Fortunately, instrument manufacturers have made great strides in this regard in recent years, but it is important that potential buyers check the availability and responsiveness of the product support offered by suppliers, along with the general maintenance requirements of instruments.

For PerkinElmer’s Carola Schmidt, one of the most important issues pertains to media viscosity: “Different media have different viscosities. If not accounted for, viscosity variation can reduce pipetting accuracy. Every time a medium is incorporated into an HTS workflow, pipetting accuracy should be validated. Without validation, the actual media volumes pipetted can be inexact, leading to unreliable results. Such inaccuracies can easily harm an institution’s scientific reputation.”

The third factor that is vital to the successful implementation of an automated liquid handling system is software, which needs to be sufficiently user-friendly to enable the novice user to perform basic operations, while still allowing those with the expertise to access more advanced features and tools. “Most HTS systems need automated liquid handlers to be fully integrated with multiple devices, such as acoustic dispensers, high-content imagers and readers. This can make data tracking and structuring throughout the whole workflow a major challenge. There is, therefore, a growing need for software infrastructure that can assist

users with data handling to facilitate data exploration,” noted Dr Rémi Magnan at Tecan.

The miniaturisation of HTS workflows

Miniaturisation is one of the main current trends in drug discovery. Harry Forsyth at Analytik Jena explained: “Lab space is at a premium in today’s environment, with the cost per square foot increasing rapidly every year, especially in the major technology hubs. This means that scientists are searching for instrumentation that provides optimal performance but takes up the smallest possible amount of space. Our FeliX liquid handling platform is designed to address this need, providing an excellent solution for researchers looking to optimise their laboratory space. In addition, the FeliX system is open and modular, so it can be combined with multiple systems, robotic arms, stackers, hotels and many other components, creating an HTS solution tailored specifically to our customers’ needs.”

An additional benefit of miniaturisation for HTS workflows is that it allows laboratories to increase their throughput (ultra HTS), productivity and efficiency. More samples can be processed within the same footprint while requiring less samples and lower reagent volumes. “Cost savings are realised through the reduction in the volume of reagents needed in the workflow,” commented Carola Schmidt. This is a particularly important issue because the reagents that are increasingly used in drug discovery are becoming more expensive and are often only available in very limited amounts. Without miniaturisation, the large-scale screening of these precious reagents may simply be impossible. But reducing the demand of these reagents is not the only benefit here. “Miniaturisation also reduces the amount of biohazard and plastic waste, which has significant environmental benefits, as well as cost savings,” added Schmidt.

Overcoming new challenges with miniaturisation

The drive for miniaturisation brings new challenges for liquid handling, and instrument manufacturers are adopting a variety of approaches to solve the issues. The first of these is achieving consistent and precise liquid handling with volumes in the nanolitre range or lower, which presents difficulties such as overcoming static forces that can prevent proper dispensing into recipient wells.

“There are several products designed to address the issue of precise liquid handling at low volumes,” commented Kevin Truempi at Agilent. “Our Agilent Bravo is a screening workhorse that

Spread the word: How innovation in life science PR is improving engagement

By Helen Stewart-Miller, Director of PR Services, and Clare Russell, Managing Director, BioStrata

Life science is an ever-changing sector, with companies embracing new technologies in order to stay ahead of competitors. Not only has this facilitated the new products and services being released at an impressive rate by R&D teams, but leading companies are also using technological innovation to drive progress across other business functions, including marketing communications and public relations (PR).

In the increasingly-competitive life science landscape, reaching your prospects with the right information at the right time is more important than ever before. In recent years, marketing automation has become commonplace. As part of a strategic campaign, technologies such as HubSpot are helping life science companies to adeptly manage the buyer’s journey and serve compelling content in a more targeted way in order to attract leads, nurture prospects and delight existing customers.

Automated press release distribution services – offered as standalone solutions or as part of mainstream media database platforms – sought to replicate this success for PR by sending out news to the media at the click of a few buttons. However, as generalist services these were often unable to target the right media contacts with the right news. This was further compounded as the databases powering these services struggled to keep up with the sheer number of niche life science publications and manage the subtle changes in editors’ briefs over time. As such, press releases did not always reach the most relevant contacts, missing their potential for publication and therefore being seen by intended prospective customers.

In response, the team of life science PR experts at BioStrata developed Life Science Newswire, a targeted press release distribution service that helps companies secure media coverage to increase visibility, build credibility and improve brand awareness within key communities. The easy-to-use service targets only relevant geographical regions and vertical markets, so organisations can reach specific industry journalists and editors with the news they will want to report to their readers. With improved metrics to measure engagement, uptake and coverage, the service fine-tunes which editors receive each announcement based on their unique interests.

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delivers precise liquid handling for 96- to 1536-well plates. The instrument is equipped with positive displacement syringes for very precise pipetting. Furthermore, the software controlling the robot includes a state-of-the-art scheduler that enables timed incubations to be carried out, which are a requirement for many screening assays today.”

Tecan has tackled the handling of very low volumes by harnessing HP’s proven thermal inkjet technology to dispense precise volumes of liquids. “Tecan’s D300e Digital Dispenser can dispense volumes as low as 11pL and up to 10µL directly from the stock solution into the assay plate. The dead volume can be as low as 2µL, which is especially important when compounds are only available in small quantities. The main application of the D300e is for assay development and target validation, where high flexibility and easy operation with little programming are paramount,” explained Dr Rémi Magnan.

Analytik Jena manufactures liquid handling systems with a proven tip sealing technology that enables users to perform high precision HTS with volumes in the sub-microliter range. “Our tip sealing technology works by applying a uniform pressure that partially embeds the top of each tip into a silicone mat, making an airtight seal. This also ensures uniform tip length for enhanced pipetting performance and liquid transfers into dry or high-density microplates,” said Harry Forsyth at Analytik Jena.

In short, many of the challenges of low-volume automated liquid handling come down to reliability – for HTS results to be valid, the accuracy and repeatability of dispensing are essential. For example, an error of +/-200nL can be fairly insignificant (1%) in a 20µL dispense. However, for a 1µL dispense, a volumetric error of the same magnitude translates into a huge 20% error. “Add to this the need to handle more challenging reagents as assays get ever more complex, and it becomes difficult for liquid handlers to perform at the levels required by screeners to give robust data,” said Joby Jenkins at SPT Labtech.

SPT Labtech addresses this issue of low volume dispense reliability with direct piston-driven positive displacement technology. This approach eliminates the reliance on valves, pumps, pressure, air and system liquid displacement to provide highly reliable and accurate dispensing, irrespective of liquid viscosity, surface tension or environmental conditions.

Advancing tomorrow’s HTS workflows

While miniaturisation and low-volume handling are the dominant trends today, given the rapid

advance of technology, manufacturers must ensure their instruments have the flexibility to adapt to ever-changing requirements. For example, PerkinElmer has identified the need for increased standardisation, a development that will become ever more important as the prevalence of collaborative multicentre studies continues to grow. Although these diffuse networks play a vital role in advancing drug discovery research, they can present difficulties due to laboratory-specific differences in workflows.

“The incorporation of automated liquid handlers into HTS workflows dramatically improves lab standardisation with automated sample tracking and Laboratory Information Management Systems (LIMS) integration. PerkinElmer’s liquid handling workstations facilitate sample tracking by incorporating automated barcode scanning into every step of sample processing. Samples are placed into a PerkinElmer automation solution where they are scanned by the barcode reader, which communicates with the LIMS and then processed according to predefined work orders, allowing labs to import data into management systems easily,” commented PerkinElmer’s Carola Schmidt.

In a similar vein, Agilent offers automated plate barcode labelling and sealing with its BenchCel Workstations. “All our automation products can be interfaced with LIMS and can output pre-configured email user notifications, tracking sample and progress to minimise manual entries and idle time,” noted Kevin Truempi at Agilent.

There is a growing tendency for HTS workflows to include more and more integration of third-party devices. For such systems to operate effectively, good communication between these devices and the liquid handler is vital. Tecan’s latest generation liquid handler, Fluent®, has been designed to provide a high degree of flexibility to accommodate the integration of a broad range of third-party devices. Tecan’s specialty integration solution, Labwerx™, allows users to integrate a number of modules and devices with the automated liquid handler, allowing complex customised systems to be built to accommodate the needs of modern HTS workflows.

The ever-increasing complexity of screening assays in the drug discovery field has started to shift the focus away from speed-based performance towards data integrity and system-based flexibility. “The ordering and timing of reagent additions and general volumetric performance are critical for more involved assays, and therefore the deployment of more sophisticated liquid handling technologies will become prevalent. To address

these issues, SPT Labtech's dragonfly® discovery is not only equipped with positive displacement dispensing technology but also several onboard timing-management features for time-course reagent additions, as well as per-plate incubation steps, providing tighter control without the reliance on robotic integration schedulers," said Joby Jenkins at SPT Labtech.

"Our vision is for a liquid handling technology to be used right the way through the drug discovery process – from assay development and validation through to HTS and into the lead optimisation stages – eliminating transition pain points and ensuring that screening data is as robust as possible. This was not an option with earlier instrumentation, but the next generation of low-volume liquid handlers, such as dragonfly® discovery, are enabling users to realise this vision," added Jenkins.

Commercially-available automated liquid handling systems

The latest advances in automated liquid handling systems are driving ever-greater precision in low-volume liquid handling and expediting HTS workflows for drug discovery.

Summarised below are some of the most innovative systems available on the market today:

Agilent Bravo automated liquid handling platform: Agilent's Bravo is a highly-flexible automated liquid handling system that fits easily on a small benchtop or within a laminar flow hood. Positive displacement syringes allow for ultra-precise pipetting of volumes ranging from 300nL to 250µL in 96-, 384- and 1536-well microplates. Extensive protocol optimisation is possible with the platform's ability to pick up tips using a single barrel, row, column or array of barrels. The Bravo platform is designed for user-friendly interaction, which facilitates rapid and intuitive creation of automated assay protocols.

Complementing the Bravo Platform is Agilent's BenchCel Workstation, a compact, automated microplate handler to facilitate more efficient barcode labelling, sealing and centrifugation. The workstation boasts a rapid eight-second stack-to-instrument transfer time and can handle up to 60 standard SBS microplates per rack for expedited microplate set-up and management (Figure 1).

Analytik Jena CyBio FeliX: Analytik Jena's CyBio FeliX is a fully-automatic, multi-channel pipetting system designed to optimise liquid handling protocols. With the system's unique compact design featuring 12 positions across two platforms, the

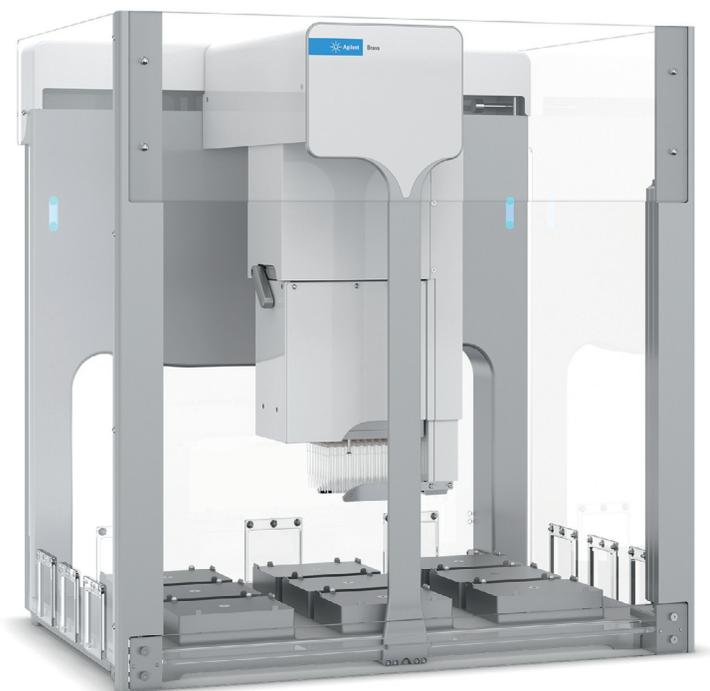


Figure 1: The Agilent Bravo automated liquid handling platform can be used to easily automate a wide range of sample preparation protocols, boasting an extensive selection of accessories and intuitive VWorks control software



Figure 2: The Cybio FeliX automated liquid handling robot is built to optimise work processes, with a unique double platform design to save valuable laboratory space



Figure 3: The JANUS® G3 portfolio from PerkinElmer delivers flexibility for sample preparation, with both dedicated, application-specific workstations and personalised automation solutions available



Figure 4: The Tecan Fluent® offers a state-of-the-art automation workstation for laboratories looking to streamline workflows and optimise assay precision and consistency

CyBio Felix offers functionality with a minimised laboratory footprint. Easily exchangeable pipetting heads and automatic liquid handling adapter-changing capabilities provide users with a highly flexible pipetting solution, and the modular design allows for easy integration with other automation systems for a complete and optimised HTS workflow (Figure 2).

PerkinElmer JANUS® G3, Sciclone® G3 and Zephyr® G3 liquid handling workstations: Perkin-Elmer offers a comprehensive range of automated liquid handling solutions across the JANUS® G3, Sciclone® G3 and Zephyr® G3 workstation series. PerkinElmer's liquid handlers are both modular and scalable and can be modified from benchtop liquid handlers to fully-automated explorer™ G3 workstations by integrating them with other workflow components. This allows PerkinElmer to deliver flexibility in throughput, capacity and dynamic volume range, allowing customers to move from benchtop solutions to fully-automated workflow solutions as their needs change.

The JANUS® G3 series provides a selection of deck sizes and pipetting arms for flexible sample preparation. The workstation can accurately dispense volumes from 0.5µL to 5,000µL, with further customisation possible via a range of workstation accessories.

PerkinElmer's Sciclone® G3 workstation is another highly-flexible liquid handling solution, with open-deck architecture for easy incorporation of additional components and compatibility with bulk reagent modules, an on-deck microplate shaker and more.

Meanwhile, the Zephyr® G3 workstation provides a compact automated liquid handling solution ideal for the workbench. Accessible from all sides, the system allows for rapid replacement of consumables and easy reconfiguration of accessory components (Figure 3).

Tecan D300e Digital Dispenser, Fluent® and Labwerx™: Tecan is driving assay miniaturisation with the D300e Digital Dispenser. Based on the proven thermal inkjet technology from HP Inc, it can dispense volumes from 11pL to 10µL directly from the stock solution into the assay plate. The dead volume can be as low as 2µL, helping to preserve limited supplies of reagents. The intuitive D300eControl software expedites experiment setup with the ability to copy and paste existing plate layouts directly from Microsoft Excel, and it is capable of using SLAS/ANSI format 12-1536-well



Figure 5: The dragonfly® discovery liquid handler from SPT Labtech provides scientists with a system for developing complex assays with ease, allowing for validation and screening in a reliable and cost-efficient manner

plates, allowing for easy transfer of manual 96-well assays into higher density plate formats.

Tecan's latest liquid handler, Fluent®, has been built for flexibility with a modular, open design for easy configuration of each component. The system can rapidly change between 96- and 384-channel formats, and the Flexible Channel Arm™ offers a choice of air- or liquid-displacement technology. The arm can accommodate either fixed or disposable tips to accurately dispense volumes from <500nL to >5mL. In addition, Tecan Labwerx™ creates reliable customised end-to-end solutions to address laboratories' ever-changing needs (Figure 4).

SPT Labtech dragonfly® discovery automated liquid handler: SPT Labtech's newest liquid handling platform, the dragonfly® discovery, has been designed to reduce assay development time and greatly improve HTS efficiency, as well as enabling hit-to-lead and lead optimisation workflows. The easy-to-use system boasts precise non-contact dispensing across a broad dynamic range (200nL to 4mL) from up to 10 independently-controlled positive displacement disposable tips. The system also features a highly visual and easy-to-use software with in-built time-management features for automation of time point experiments, meaning tighter control and maximised walk-away time (Figure 5).

Conclusion

The latest advances offered by current automated liquid handling systems are benefiting a broad range of drug discovery applications, while continued enhancements are driving improvements in the precision, accuracy, speed and repeatability of workflows. In turn, these developments will have a significant impact on reducing assay development and transition to HTS times, helping to deliver dramatic reductions in drug discovery timescales. **DDW**

Tecan's D300e dispenser as well as customised versions of Fluent® are for research use only and might not be available in your country.

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