

# FASTER, SMALLER, SMARTER

## *How advanced automated liquid handling systems are reshaping drug discovery*

Once the domain of high-throughput screening (HTS) applications, automated liquid handling systems are now used ubiquitously in drug discovery and have been fundamental in increasing throughput, driving efficiencies and improving standards of accuracy and reproducibility in pharmaceutical and biotechnology workflows. This roundtable considers some of the latest advances in liquid handling technology and the impact they are having on drug discovery.

**D**rug discovery has undergone a revolution over the past two decades, thanks in large part to the widespread adoption of automated liquid handling. Driven by a competitive need to maximise throughput and increase productivity while ensuring the highest levels of accuracy and reproducibility, automated liquid handling systems have been adopted across the entire pharmaceutical and biotechnology pipeline.

Improvements in the scale, speed and quality of workflows enabled by automated liquid handling have not only helped to reduce timescales and deliver results faster, they have also made drug discovery more efficient and systematic. Use of automated liquid handling in assay development, for example, is essential for the methodical testing of multiple conditions to ensure robust assays are put forward for screening applications. Automated liquid handling systems have also been vital to simplify the creation of complex multi-parameter experiments in a reproducible, reliable and robust manner, while freeing highly-trained scientists from manual lab-work to focus on more skilled tasks, such as the analysis of data and planning of experiments.

The remarkable scale and speed at which liquid handling tasks can now be performed have accelerated a shift towards biotechnology-derived therapeutics and new approaches to personalised medicine. Advanced high-throughput techniques, such as next-generation sequencing and genomics-based target discovery, demand operation at a rate and on a scale that can only be achieved using automation.

Automation in liquid handling workflows has long been critical for drug discovery. Today, in the era of genomics, next-generation sequencing and personalised medicine, it is proving more important than ever as a tool for accelerating the search for safe and effective therapeutics.

### **More precise and accurate low-volume liquid handling**

While performance criteria once focused squarely on speed, capacity and throughput, recent advances in liquid handling technologies, automation software and robotics have led to the development of a new generation of platforms that offer exceptional accuracy and precision even when dispensing the smallest volumes.

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**Figure 1**

The Echo® 655T acoustic liquid handler can be used to eliminate compound loss, cross-contamination, carryover or leachates in liquid handling workflows across drug discovery and fundamental research



Many of these improvements have directly resulted from the development of liquid handling technologies that are specifically designed to accurately transfer liquids on the nanolitre scale or below. The latest positive displacement pipetting systems, for example, which employ highly accurate, yet low-cost, disposable pistons to dispense liquids, can now handle a wide range of liquid types and a broad range of volumes. Furthermore, because the pistons are only used once, they ensure consistent accuracy while eliminating the potential for contamination, clogging or carryover, reducing downtime.

“Accurately and reproducibly transferring and dispensing low sample volumes has traditionally been a challenge, especially for less tractable liquids such as viscous fluids,” says Joby Jenkins, Director of Product Strategy at TTP Labtech. “Next generation liquid handling technologies, such as automated positive displacement pipetting systems, are enabling scientists to cover both lower volume ranges and a wider variety of liquid types ranging from highly viscous to highly volatile, meaning they can now be used for more challenging applications where once manual pipetting was required.”

Other innovative dispensing technologies are eliminating contact between the instrument and liquids completely. Acoustic liquid handling, which relies on the technique known as acoustic droplet ejection (ADE), is a relatively new approach to liquid handling that uses acoustic energy to transfer solutions in nanolitre increments. As this technology propels precisely-sized droplets from a source plate to a high-density microplate suspended above it, the liquid does not come into contact with any other surface, avoiding the possibility of cross-contamination, loss of material or exposure to leachates.

Importantly, while early acoustic liquid handling platforms could only support a limited set of liquid and container types, recent design improvements mean that modern systems are compatible with a much broader range of liquids. These systems are enabling ultra-high throughput applications and allowing researchers to accomplish more at considerably lower costs, without compromising on quality.

However, it's not just novel dispensing technologies that are helping to drive improvements in liquid handling precision. Advances in automation software and control systems have also had a substantial impact on performance.

“Ten or even five years ago, automated liquid handlers struggled to deliver the level of pipetting precision we now take for granted,” says Dr Eric Niederkofler, Application Leader, Affinity and Automation Consumables, at Thermo Fisher Scientific. “Modern sensor-integrated systems are capable of achieving exceptional accuracy, in part due to innovations such as software applications that can calibrate pipetting performance based on parameters such as liquid and tip type, volume range and mode of dispensing.”

Thanks to improvements in dispensing design and automation software, pharmaceutical companies are bringing automation into drug discovery workflows where previously manual pipetting was required, helping to unlock potential research solutions and push past drug discovery hurdles with greater speed.

### **Precision liquid handling is enabling process miniaturisation**

The significant improvements in the low-volume accuracy and precision achieved by modern liquid handling systems are not just helping to boost confidence in experimental findings. The ability to work with fluids at the nanolitre or even picolitre scale is helping to miniaturise workflows and is driving efficiencies even further.



“Those engaged with drug discovery workflows typically face two key challenges – how can I achieve accurate results, and how can I do this as efficiently as possible,” notes Randy Dyer, Director of Product Marketing at Labcyte Inc. “Non-contact liquid handling techniques, and in particular acoustic liquid handlers, are allowing scientists to obtain accurate data with fewer steps and much less sample and reagent. The time and cost saved from the increased efficiency has a positive impact on workflows that occur upstream or downstream of where acoustic liquid handling is used and can lead to the development of entirely new approaches.”

The latest generation of liquid handling systems is also enabling the routine use of much higher density microplates, such as 1536-well formats. Accurate, reliable and consistent liquid handling on this scale has opened up a wealth of applications for ultra-high-throughput experimentation within drug discovery, helping pharmaceutical companies find innovative drugs faster and more resource-efficient.

### Commercially-available automated liquid handling systems

Modern liquid handling systems are enhancing throughput, improving accuracy and minimising the potential for human error in drug discovery workflows. Here we provide a summary of some of the key products available on the market:

The **Agilent** Bravo Automated Liquid Handling Platform is a compact system that can fit in a laminar flow hood. The Bravo platform utilises a choice of four pipette heads to accurately dispense volumes from 300nL to 250µL in 96-, 384- and 1536-well microplates, with disposable tips for specific applications. The swappable pipette heads, user-configurable deck and ability to pick up tips using a single barrel, row, column or array of barrels allow easy customisation to meet specific assay needs. The system’s open design allows access from all sides, facilitating system integration as well as standalone use.

With an even smaller bench footprint, the Agilent Vertical Pipetting Station’s unique eight-microplate position design features a two-axis positioning stage that allows it to integrate seamlessly into automation systems. The vertical pipettor uses high-accuracy heads to dispense volumes from 100nL to 250µL in 96-, 384- and 1536-well microplates with a positioning precision of  $\pm 0.025$ mm. The system delivers industry-leading speed, with an average cycle time of approximately 10 seconds for a microplate transfer and can

pipette while other microplates are changed to further reduce assay time.

**Labcyte’s** Echo Liquid Handlers use sound energy to achieve a fully non-contact acoustic liquid handling workflow from sample storage to assay-ready plates, eliminating compound loss, cross-contamination, carryover or exposure to leachates. The Echo® 655T Liquid Handler is Labcyte’s most advanced system and is designed to support a wide range of applications in drug discovery and fundamental research. The system provides exceptional precision and is capable of accurately transferring volumes as small as 2.5nL from 384- and 1536-well plates, as well as 96-tube racks. The Echo® 655T system is compatible with the FluidX™ AcoustiX™ Sample Tube technology, developed in partnership with Brooks Life Sciences. The AcoustiX tubes support more efficient sample utilisation and enable ultra-high-density storage.

When fully automated workflows are required, the Echo® 655T system can be integrated with Labcyte’s configurable Access™ Dual Robot System to achieve optimal levels of throughput. The compact and ergonomic platform design features docking modules, turntables, retractable shelves and drawers, and can be supplemented with environmental management features to protect samples from evaporation or hydration.

**PerkinElmer** offers a broad range of automated liquid handling solutions that can be configured according to the needs of users’ specific applications. The JANUS® G3 series of automated liquid handling workstations is comprised of four different models (the Mini, Standard, Expanded and Integrator) that vary in terms of deck size and pipetting arm technology. With the options of the Varispan™ arm technology and/or automatic interchangeable 96 and 384-well Multidisplacement Technology (MDT), users have customised flexibility in throughput, capacity and dynamic volume range.

PerkinElmer’s Zephyr® G3 range of liquid handling workstations includes compact systems with a small footprint, making them well-suited for bench operation with a focus on Next Generation Sequencing. The open deck design enables easy access from all four sides, allowing rapid replacement of consumables. The Zephyr® G3 series offers a range of useful features, including the ability to hold lids while dispensing, row- and column-wise serial dilutions, partial tips loading, barcode identification and seamless integration capabilities, to simplify liquid handling workflows and

**Figure 2**

The D300e Digital Dispenser can be used in assay development and target validation applications, where high flexibility and easy operation with little programming is needed



maximise efficiency. These attributes provide the flexibility in the Zephyr<sup>®</sup> G3 NGS solution, combining the features with ready to use NGS methods, making the Zephyr<sup>®</sup> workstation an application specific solution.

Tecan is driving assay miniaturisation with the D300e Digital Dispenser. Based on proven thermal inkjet technology from HP Inc, it can dispense volumes of between 11pL and 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 D300e Digital Dispenser's main application is not HTS, rather assay development and target validation, where high flexibility and easy operation with little programming is needed. The intuitive D300e control software allows users to run experiments in minutes, thanks to the ability to transfer existing plate layouts from Microsoft Excel into the software. The built-in software wizards not only facilitate dose-response experiment set-up but also the layout of complex assays, such as drug-drug synergy assays with two or more compounds, with the possibility to normalise and even randomise the plate layouts to reduce edge effects. The platform is capable of using SLAS/ANSI format plates with 12 to 1536 wells, which easily accommodates the transfer of manual

96-well assay into higher density plate formats for HTS assay development.

The Thermo Fisher Scientific Versette<sup>™</sup> Automated Liquid Handler is a compact and flexible system designed to meet the needs of most laboratories. With a choice of 96- and 384-channel pipetting heads for volume ranges from 0.5 to 300µL, and featuring user-friendly programming, the automated system is well-suited for a broad range of liquid handling applications, including the replication of 96- or 384-well plates, the stamping of microtiter plates and serial dilution.

The Thermo Scientific Multidrop<sup>™</sup> Combi Reagent Dispenser offers fast dispensing and high-throughput operation and can handle a wide range of microplate sizes and volume ranges. Delivering precise liquid dispensing over a 0.5 to 2,500µL range and accommodating 6- to 1536-well plates, the automated system is highly flexible and uses eight-channel detachable and autoclavable dispensing cassettes that are standard across the Multidrop<sup>™</sup> range. The system features an icon-based graphic display that makes it easy to use and programme, and enhanced functionality and flexibility can be achieved when used with Thermo Scientific FILLit software.

TTP Labtech's mosquito<sup>®</sup> automated liquid handlers use individual pistons, rather than air gaps or



system liquid, to consistently and accurately dispense volumes from the nanolitre to the microlitre range. Each system is built for specific laboratory applications. The mosquito<sup>®</sup> HTS, for example, is designed for cost-effective assay miniaturisation and provides precise multichannel pipetting from 25nL to 1.2µL. The user-friendly instrument maximises sample use through ultra-low dead volumes as small as 0.2µL, enabling high speed serial dilutions and allowing a full set of dose response curves to be prepared in minutes using less than 2µL of stock solution. The mosquito<sup>®</sup> Xtal3, by contrast, is designed for protein crystallisation applications and facilitates all of the common crystallisation screening techniques, including hanging drop, sitting drop, microbatch and seeding or additive screening plate preparation.

TTP Labtech's newest liquid handling platform, the dragonfly<sup>®</sup> discovery, has been designed to reduce assay development time and 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.

### User-friendly liquid handling systems are removing barriers to adoption

Across all areas of drug discovery, pharmaceutical companies remain under pressure to do more with less, using streamlined workflows that shorten the time required to turn ideas into innovations. Faced with the need to adopt the most efficient techniques, laboratories and their staff can find themselves with an overwhelming variety of new tech-

nologies and methods that require specialist expertise to operate. Flexible, easy-to-use liquid handling systems that can be implemented as quickly as possible are therefore highly prized.

“Within the labs, operators are also being tasked with more instruments, more assays, and more automation,” says Hal Wehrenberg, Head of Product Management at Tecan. “To keep up with these demands, liquid handling and automation systems must actually help users through intuitive interfaces, rather than creating an additional layer of complexity. Ideally these interfaces should be customised to the exact needs of the lab and convey information visually to make workflows as easy-to-use as possible.”

However, automated liquid handling systems have traditionally been perceived as challenging to use, with difficult-to-navigate user interfaces posing a considerable barrier to their broader adoption. Fortunately, many equipment vendors have listened to the scientific community, with some of the latest generation of automated liquid handling systems being easier to operate than ever before. These systems are providing much greater ease of access, while still maintaining the powerful functionality that is required to get the most from complex automated workflows, ultimately helping more companies access the operational efficiencies and improved measurement accuracy associated with increased automation.

“Not so long ago, you’d find many laboratory technicians being overwhelmed by the look and feel of the user interface of automated liquid handling systems. Even with graphical components to help with the navigation, user interfaces were not always flexible enough to allow minor alterations

**Figure 3**  
Easy-to-use, form-based user interface on the Agilent AssayMAP Bravo Platform



without requiring a certain amount of programming,” says Maryann Shen, Automation Solutions Marketing Manager at Agilent Technologies. “Some of the recent instruments include pre-programmed workflows with a user-friendly interface making it easier and more routine for laboratory technicians at all expertise levels to operate. These systems also include pre-programmed utilities, such as normalisation, serial dilution, reformatting and other typical liquid handling tasks.”

Ensuring a low barrier to operation is critical for maximising the efficiency gains automated systems offer. As such, many instrument vendors have tried to minimise usability challenges by placing an increased focus on providing training and support.

“Some scientists are unaware of the resources available to them once an instrument has been installed and the supplier is no longer on site,” says Mark Dupal, Global Portfolio Manager of Automation and Microfluidics, Applied Genomics, at PerkinElmer. “Access to support is incredibly important, and that’s why our team of field application scientists will spend the time to understand the researcher’s various workflows, provide appropriate training and remain available as a resource.”

The latest improvements in ease of use, alongside the remarkable advances in low-volume precision offered by modern liquid handling systems, are helping to enable the benefits of automation to be felt across a much broader range of drug discovery applications. These ongoing enhancements of automated liquid handling systems are driving improvements in the speed, accuracy and consistency of workflows right across the drug discovery pipeline. **DDW**

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