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Making the move to automated liquid handling:

A Buyer's Guide

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Introduction

As a scientist working in a lab, you feel the strain of repetitive, manual liquid handling processes day to day. You're a human, not a machine however, you feel like you need to perform like a robot with long hours and no mistakes as the standard in order to achieve targets and deliver results.

You may have used automation in some capacity but you're aware your lab could be doing more to stamp out inefficient processes and techniques, replacing them with more reliable and consistent solutions that reduce impact on labour.

Despite limitations such as budget, equipment and time restraints, you're optimistic about introducing automation and will do everything you can to get buy-in from senior leaders.

With this in mind, it's important that your business case for automation is a strong one. You don't want to risk being the internal risk taker who has introduced an expensive and unreliable paper weight. You need to ensure you recommend the right technology to your management team and you need precise information and data to get you there.

In this guide, we discuss the things you should consider as part of your business case when purchasing automated liquid handling equipment and how to make the transition as smooth as possible.

We highlight the common manual challenges and how to overcome them and look at workflows that benefit from automation so you can make an informed decision about how to proceed and how it can best work for you.



Manual pipetting challenges and how to overcome them with automated liquid handling

Unreliable results

Humans contribute a significant source of error in laboratory pipetting. Pipetting too quickly, failing to pre-wet the tip, unnecessary tip wiping, pipetting at an angle or using the wrong tips altogether causes unreliable results. All of these challenges result in wastage and when you have irreplaceable samples and expensive reagents, errors in manual pipetting are costly.

Automated liquid handling eliminates human error without the need to invest in additional staff-training and lab resources. Automated instruments ensure pipetting occurs consistently and it also minimizes samples wasted on needing to carry out experiments the second time round. All of these benefits make for improved data quality and additional data points.

Wasted time

Scientists dedicate a large part of their day to manual pipetting. This is poor use of your time and overall laboratory resources, time that could be spent more productively.

'Pipetting activities can take up to 88% of the workday for certain laboratory staff. This puts current estimates of pipetting activities between 1,200 and 1,900 hours per year.'

With lab automation in place, you are free to do other, more meaningful activities in the lab—like data analysis, experiment design, and writing up results for publication.

Health concerns

Scientists carrying out manual pipetting tasks are at risk of repetitive motion injuries, specifically strain of wrists, arms, shoulders and awkward postures. These types of injuries develop over time and occur when muscles and joints are stressed and there is restrictive blood flow. Staff are also at risk of exposure to hazardous materials through manual pipetting.

'Pipetting more than 2 hours per day puts users at a 60% risk of suffering hand and shoulder ailments.'

Automation eliminates these issues associated with manual pipetting.



Inability to scale processes and increase throughput

When time and resources are spent on manual pipetting, it's difficult to scale processes and increase throughput without investing more resources and budget. Automated pipetting allows you to standardize your processes. Since liquid handling robots can outperform even the most skilled operators, the ability to scale and increase throughput can be made a reality.

Lab automation is not about replacing humans with robots. It's about relieving laboratory staff from tedious manual tasks so they can focus on the science.

Benefits of automated liquid handling

Consistent delivery of samples and reagents is essential for many delicate techniques employed in today's laboratories. Liquid handling equipment distributes a certain volume of liquid from a source container and dispenses this liquid to the destination container once it has been appropriately repositioned. The fluid being transferred, often referred to as the sample fluid, is most commonly held in tips. These tips can either be permanent features of the liquid handler or disposable pieces.

Drug discovery and genomics have massively evolved over the past two decades, and much of this is down to automated liquid handling. From individual tips to large-scale automated liquid handling involving multiple tips, channels, robots and large workstations, advancements in technology have enabled liquid transfer solutions to progress substantially.

The ability to maximize throughput and increase productivity whilst ensuring the highest levels of accuracy and reproducibility are driving the adoption of automated liquid handling in the pharmaceutical and biotechnology space.

The most common benefits of automation include:

- Saving time
- Increasing throughput by doing the operation faster or doing multiple liquid handling at once
- Improved accuracy from hand pipetting
- Minimized health risks for laboratory staff



Things you may not have known about automated liquid handling

- You don't need an entire room dedicated to the instrument
- Many instruments sit on a bench space and have a footprint of one third square meter
- You don't need experienced in-house automation staff
- With the support of lab service providers to set up applications, novice users can run systems
- Getting scientists trained up on the new instrument is not as difficult as you may think
- Once protocols have been developed, it can take as little as 10 minutes to 2 hours to train users

Building a business case for automation

Building a business case for lab automation will be key in proving to your stakeholders that you're making a sound investment. These next sections will help you structure what your business case should look like.

What are you looking to achieve?

First things first. What's your motivation for investing in automated liquid handling? What are you trying to achieve? Some of the most popular reasons are to:

- increase throughput;
- miniaturize assays into formats not possible by hand;
- improve assay reproducibility;
- reduce the variability of results between scientists;
- save valuable time and costs;
- minimize reagent use;
- relieve the boredom from the repetitive nature of routine assay preparation;
- reduce the potential for staff repetitive strain injury;
- free up resources for other tasks.

There are many benefits to be realized from automated liquid handling but listing them based on importance will help you prioritize your checklist.

What do you want to automate?

In addition to outlining what you're trying to achieve with automated liquid handling, you need to highlight in your business case what workflows you want to automate. It may seem obvious, but it's a good idea to really dig deep into this.

Be mindful that it's not always best to automate everything and it certainly shouldn't be carried out all in one go. A step by step approach will enable you to deliver innovation that delivers consistency and reliability. Identify the problem areas first and start by automating these.

Ask yourself these questions when thinking about what you'd like to automate.

Does the liquid handling solution ***need to be versatile***, taking the strain in as many applications as possible, or are you ***looking to fill a niche gap*** in your liquid handling needs?

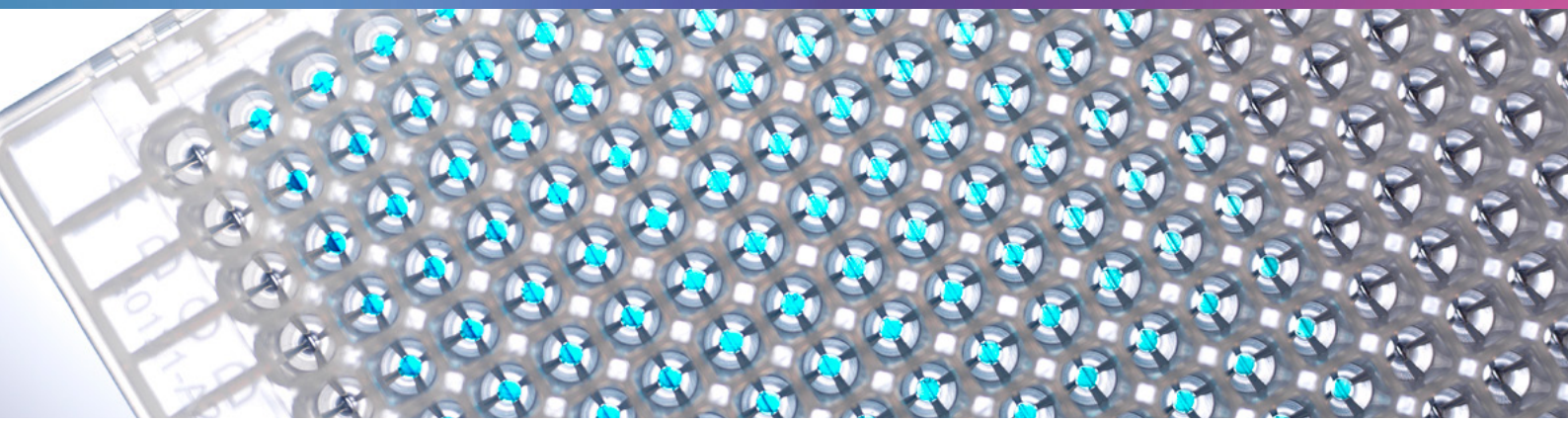
Are you ***primarily concerned with dispense performance,*** so the absolute accuracy and precision of the liquid handling steps is super critical, or do you ***need it to deliver liquids to extremely precise locations*** on a plate e.g. when performing serial dilutions in low volumes, or for protein crystallography?

How much liquid will you transfer? (the optimal volume for automation is typically 1-1000 µL but some automated systems are able to reach nL or even pL volumes).

How many steps are involved in the liquid handling process and how time consuming is it?

How many times a week do you run the workflow? If you run the workflow at least once a week, you have a good candidate for automation.

How much dead volume is acceptable? When working with the hand pipette dead volumes are close to zero. ***With automation, it is not uncommon for several mL to be lost when priming or within tubing.***



Volume and liquid type considerations

To explore the point of volume and throughput considerations a little further, you need to know how much liquid you will want to move and how fast. We previously mentioned that the optimal volume for most labs is 1-1000 µL, accommodating many typical workflows.

Do you need a small dynamic volume range because you routinely use one microplate format, or a large dynamic volume range to cater for many different microplate formats? Like hand pipettes, robots cater for different volume ranges too, so you need to match accordingly.

Automated liquid transfer systems come in 3 classes:

- classic = >1µL (air or system liquid displacement),
- sub µL (positive displacement),
- sub nL (acoustic and inkjet).

Air displacement technology

Air displacement pipetting relies on an air cushion between the pipette piston and liquid. Movement of the piston inside the pipette creates a positive or negative pressure that moves liquid in or out of the pipette tip. Air displacement pipetting is highly accurate for standard pipetting applications above 2 µL and liquids that do not have extreme viscosities and works with a simpler tip design.

Positive displacement technology

Positive displacement pipetting and dispensing is based on a piston that is in direct contact with the liquid. Mechanical movement of the piston inside a pipette tip or dispense syringe enables highly accurate and repeatable delivery of liquid volumes. Positive displacement technologies are liquid class agnostic, meaning that a diverse range of liquid viscosities can be handled without liquid class classification. It is highly accurate in the sub-microliter volume range. Using this solution allows you to continue benefiting from the accuracy of pipetting you have become accustomed to.

Acoustic technology

Acoustic liquid handlers, as the name suggests, use sound to transfer precision droplets of liquid to a target well. Like air displacement pipettes, these need to be calibrated to the viscosity of the reagents. By not using plastic tips, these devices significantly reduce the amount of waste produced by a lab. However, they are unable to transfer 'intra-plate' or handle higher transfer volume as they rely on an inverted destination plate positioned directly over the source plate which can be limiting for some applications. Additionally, in well mixing cannot be performed and some liquid classes can be difficult to handle.

Assay miniaturization and low-volume liquid handling should also be considered. Assay miniaturization has been a real driving force in the evolution of liquid handling systems.

Reducing the volumes of samples and reagents required provides cost and time-saving benefits for both the research and drug discovery industries. This reduction has meant an increase in assay range and size and as a result, you can obtain more information per screen. For example, SPT Labtech's dragonfly® discovery system can dispense non-contact volumes of 200 nL to 4 mL of any liquid class from positive displacement disposable tips into 1536-, 384- and 96-well plates, enabling complex gradients, randomized dispensing patterns and dilutions to be performed.

You should also consider liquid types. If you use liquids that are viscous, volatile and tricky to pipette, you should source a positive displacement solution.

Additionally, if you're working with cells you should consider whether you may potentially have issues with viability post dispensing, or dispenser clogging that requires sanity checking at demo. Do you need to work under sterile conditions? If so, you should check to ensure your proposed solution is small enough to reside in a hood. This could lead to additional investment if overlooked.

Always ask vendors to provide full information on the range, variance, and accuracy of their pipetting/ dispensing technology, across a range of representative liquids matched to your application, to ensure it fits with the needs of your miniaturized protocol.

Throughput considerations

The level of throughput will be an important factor to consider when buying automated liquid handling technology. This entails the number of samples you will process at once. For many scientists, increasing throughput is one of the main drivers for moving to automation, according to The 2017 Automated Liquid Handling Survey Results. The level of throughput can be defined within three categories—low, medium or high.

High-throughput screening for small or large molecules in drug discovery typically involves a single point biochemical or cell-based assay screen directed against a target or a desired phenotypic outcome. Lab automation systems made for high throughput are designed to streamline workflows from sample store, to assay plate preparation, to driving decision making data within a high throughput environment.

Low-throughput is usually best suited to labs running a few microplates or less per day. That said, for more complex applications such as NextGen Sequencing library preparation there are long protocols with multiple steps, so here even a half microplate of samples can benefit from automation.o increase the speed of pipetting for this many samples only requires a single-channel pipette or a small number of multi-channel pipettes.

Medium-throughput is generally for labs working with multiwell plates from 96 to 384 wells. Here, an 8-channel pipetting will be sufficient in increasing the speed of pipetting and will reduce manual errors.

Choosing an automated liquid handling system

Once you have evaluated what you want to achieve using automation, what workflows you want to automate and have assessed volume ranges and throughput considerations, the next step is to choose the appropriate instrument that will suit your needs.

1. Single channel pipettors

Single channel pipettors are highly flexible. As described above, this type of instrument is best suited to carry out low-level throughput. Therefore, even if they are slower than other options on the market, they are recommended if you're processing less than a few hundred samples per week. Even then, if you are regularly pipetting by column in microplates you many benefit from a multi-channel pipette.

2. 96, 384, 1,536 fixed tip array heads

96, 384, 1,536 fixed tip array heads are speedy instruments but can also lack flexibility. They can have washable pin tools or tips.

3. 8/16 channel heads with pipette tips

8/16 channel heads with pipette tips are faster than single channel pipettors and are more flexible than fixed heads. As mentioned above, they are recommended for medium-level throughput. The reason why these types of multichannel systems are more flexible is because the spacing between the channels can usually be adjusted which means a wider range of applications can be used on them.

4. Bulk dispensers

Bulk dispensers can be both single or multichannel systems. They have single or multiple reagent dispensers with varying degrees of speed and flexibility.

So, how do you decide which class is most relevant to you?

Ask yourself these questions and also consider the information you have gathered from previous sections in this guide.

- Do you need a pipetting solution for serial dilutions or plate replications (i.e. it aspirates, dispenses and mixes liquids)? If this is the case, classes 1-3 will be sufficient.
- Do you require a dispenser to deliver bulk reagents? If so, you should consider simple dispensers with low flexibility within class 4.

***Note:** If you are looking for a bulk dispenser that offers more versatility to dispense different volumes of different reagents into different wells at different times, the SPT Labtech dragonfly discovery splits class 4 into 4A (limited flexibility) and 4B (versatile) category solutions. This instrument eliminates well known assay development bottlenecks and facilitates continuity from assay development into screening.*

Once you have decided the class, you should also contemplate whether you will wash non-contact dispense heads or use disposable tips. Non-contact fixed heads offer super-fast dispensing, with throughputs that cannot be matched by systems that change tips. They don't include an ongoing consumable cost but do require routine maintenance to ensure peak performance. On the other hand, disposable tips are a consumable cost to factor in but offer peace of mind with respect to dispense performance, zero system maintenance and the utmost confidence in assay results where any potential for cross contamination needs to be ruled out.

When buying an automated liquid handling system, it is fundamental to determine just how flexible you need the handler to be. Most scientists will want a system that can evolve with the labs needs according to changes in throughput and application. Therefore, you should let your chosen vendor know potential changes so they can help you find a solution that will meet your changing demands and walk you through upgrade options should you require them.



Space, investment and maintenance requirements

Space

How much room will the instrument take up and how will people interact with it on a daily basis?

Space is often an afterthought when purchasing an automated liquid handling system, but it shouldn't be. Assessing how much space it will consume is important. For many laboratories, giving up extra bench space can often be the biggest cost for implementing automation. How the new instrument might impact researchers on a daily basis should also be considered upfront.

For many labs, 'no cross-contamination' is critical. Even though robots are less likely to contaminate samples than a human operator, how sterile a robot keeps the samples is ultimately determined by the hardware included with the robot. For those workflows requiring a greater degree of sterility, samples need to be kept in a tissue culture hood, along with other equipment to keep out contaminants. This will ultimately take up more space than you may have originally thought so factoring this component into your purchase process will be important.

Further considerations:

Is the instrument(s) small enough for two people to move by themselves if you decide to rearrange the lab? Will you require multiple arms and various accessories as time goes on that might make the instrument larger? Can you accommodate that kind of space?

Investment

The investment required to purchase an automated liquid handling system will of course depend on your requirements and the budget allocation you have. Robots on the market vary from less than $10k and go all the way up to $500k. It's important to not compromise quality by going for a cheaper option but equally, you may not necessarily end up using all the functions that a high end instrument can provide. As highlighted, it really does depend on what you need the robot to do.

It's also worth noting that you're likely to have upfront costs and further ongoing costs over a period of time. These can be defined as two types of costs associated with lab automation—CAPEX and OPEX costs.

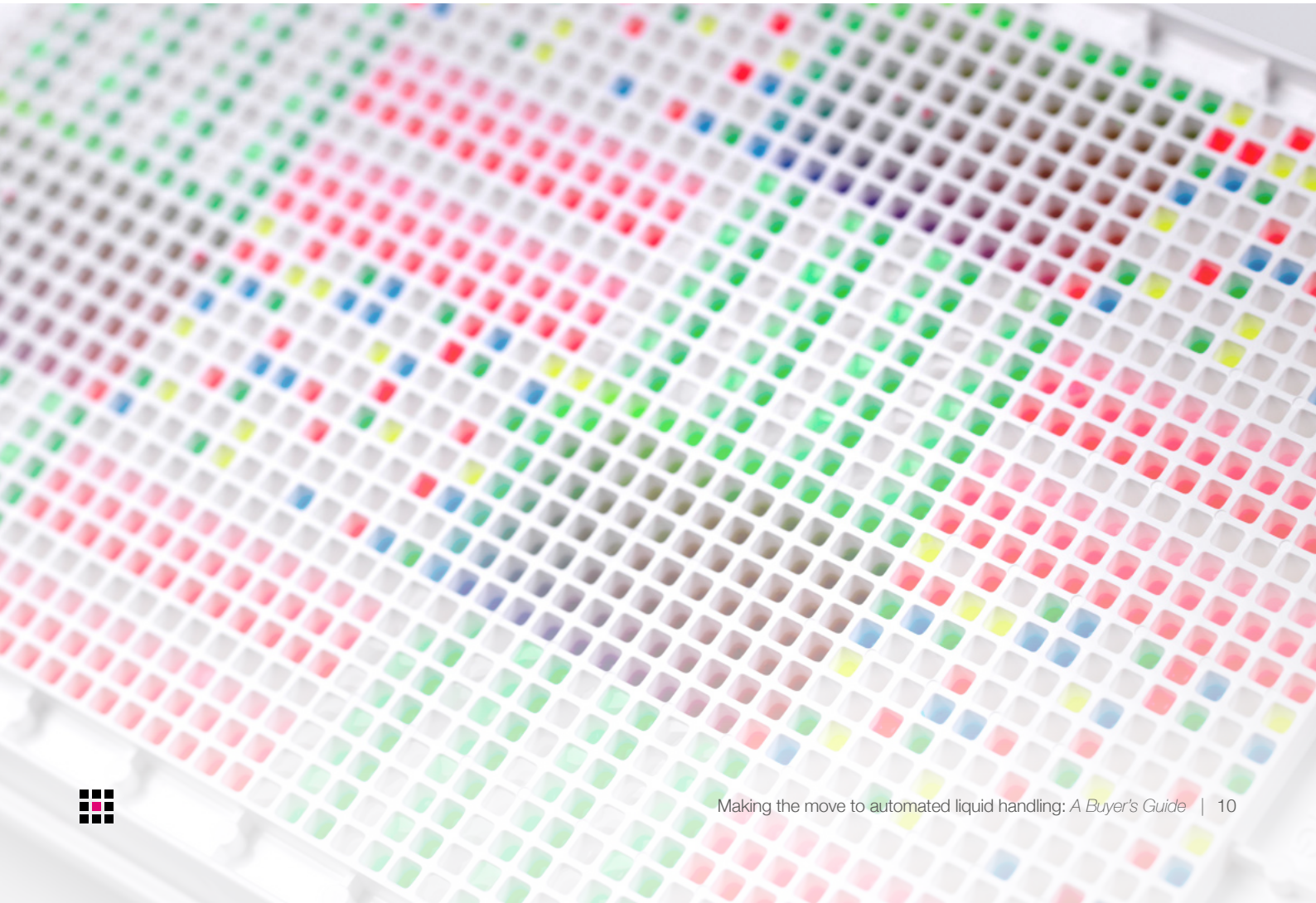
CAPEX costs are obvious and upfront. You are likely to have a budget defined that you must stick to.

OPEX costs can be significantly harder to calculate and monitor (aside from service contracts which are usually around 10% of the purchase price range). These include use of specialised consumables (e.g. cassettes, liquid sensing tips, plates). It is recommended that you know your throughput and use this to calculate and compare OPEX costs across the board.

When it comes to the cost of automation, you should take a holistic approach by calculating the return on investment over a longer period of time (Typically 5-10 years) to recognise the true long term gains. The upfront and service costs can seem high, not to mention the substantial resources required to manage the process. That's why it's important to consider all the cost related factors to determine how long it will take to see cost savings. If it turns out it's not the most cost-effective solution, is the cost of automation justified by the improvement of quality?

Maintenance

Automation will of course make your day to day life easier. However, it's important to recognize that the instrument will need some level of maintenance and you will need to carry out regular QC calibration checks. These are required to ensure the accuracy and precision of all liquid handlers, especially those containing valves. It's a good idea to ask the lab service provider at the time of sales how much you need to be involved day to day.



Running applications and support

The applications you want to automate will largely influence your decision in regards to which automated liquid handler you choose. In this section, we take a look at the most common applications used and factors to consider for each.

Automated assay development

Assay development is typically a highly manual process, both in terms of experimental design and set-up. The laborious nature of this process can limit the amount of optimization that is performed and frustratingly, assays often require re-optimizing to miniaturize into higher density microplate formats. Automated systems address this bottleneck by creating multifactorial experiments.

Software will allow experiments to be designed rapidly and with ease. Additionally, dispensing technology will enable complex combination gradients to be set-up and, with the ability to dispense from multiple channels.

High throughput screening

High throughput applications are designed for automation. Systems should have simple set up, minimal maintenance, maximum output and will provide solutions for sample management, pipetting and multiplexed assay detection that are specifically designed for high throughput automated environments. Solutions will also need to address increasingly complex experiments, ensure sample integrity, accurate data logging and robust hit identification.

Cell-based assays

The benefit of cell-based screening is to observe what compounds do to a cell, not to an isolated protein. The aim is to deliver better quality hits with a better chance of progression through drug development whilst eliminating the pursuit of poor compounds that ultimately fail.

In cell-based assays, automated liquid handlers can be used for applications such as cell plating, compound addition and reagent addition. There are various ways to automate cell-based assays, therefore, it could be viable to automate a single, small part, then several parts, separately and combine them together manually, depending on the structure of the experiment.

Next-generation sequencing

NGS library preparation

Sample preparation for Next Generation Sequencing (NGS) requires long and complex protocols with multiple liquid handling steps, making them an ideal candidate for automation.

There are many NGS sample prep kits on the market and one of the most widely used is Nextera XT (illumina inc., USA). This kits is commonly used to prepare DNA libraries based on enzymatic fragmentation of DNA samples using only very small amounts of input DNA. To ensure high accuracy and precision, most library preparation protocols recommend volumes that are within the range of manual pipettes or large volume liquid handlers. However, only a fraction of each of the preparations is then required for sequencing.
By using a liquid handler that can handle low volumes of solutions with different viscosities, smaller reaction volumes could be prepared, saving on reagent cost and sample input.

Another specialised application area of NGS that benefits greatly from automation as well as miniaturization is single cell sequencing. Single-cell sequencing involves isolating a single cell and examining its sequence information using next-generation sequencing technologies, to fully characterize cells and provide insights into cellular differences. The field of single-cell genomics is advancing rapidly, yet researchers face multiple challenges, including reproducibility, sensitivity, scalability and cost, particularly when large numbers of cells are analysed. However, automation and miniaturization has been shown to address these limitations.

Similarities and differences between automated liquid handling for drug discovery and genomics

Pipetting Technologies	Air displacement	Positive displacement	Peristaltic dispenser	Valve based dispenser	Acoustic	Inkjet
Description	Mechanical piston is used to displace a column of air to aspirate and dispense liquids	Piston (usually disposable) comes in to direct contact with the sample and moves within a tip to aspirate and dispense liquids	Uses a peristaltic action on a tube containing reagents for bulk dispensing	Use a combination of pressure and valve system to dispense reagents, usually fed through tubing from source bottles	An acoustic wave is used to transfer samples drop by drop to a microplate inverted above the source microplate	Reagents are usually pipetted into a cartridge which can then dispense them into a microplate
Good for	Aqueous samples, but more challenging volatile or viscous samples may need careful set up or may not be suitable	All types of samples work well and with little or no need to optimise a system for each liquid type	Bulk dispensing of a reasonable range of liquid types, particularly aqueous across a wide volume range	High throughput bulk dispensing where a large single or multiple reservoirs can be utilised	Robust fast non contact transfer of samples at very low volumes to microlitres	Fast, low volume (down to pL) non contact reagent dispensing
Benefits	Simple robust mechanism. Air cushion separates samples from mechanical parts and options such as filter tips minimise cross contamination risks	Assured accurate and repeatable pipetting and zero cross contamination risk if disposable tips are used	Fast and easy to set up and multiple channels can facilitate multiple reagent dispensing Generally low cost systems	Fast and manage aqueous and other less challenging reagents well Generally simple and easy to use	Has become a go to method for pL and nL sample transfer across a variety of liquid types Transfer can be verified	Capable of managing multiple reagent types with low dead volumes
Limitations	Not good for highly viscous, volatile or samples containing particulates Less accurate at low volumes	Consumables can be more expensive and fewer automated platforms feature this technology, so less choice	Highly viscous and volatile reagents are challenging and have significant dead volumes to prime the tubing Only useful for reagent dispensing	Can be prone to blockages, requiring regular maintenance and may struggle with more challenging reagents, particularly those containing particulates such as beads	Gets slower with larger volumes due to drop by drop approach and existing volume of liquid in destination plate can be a problem when inverted. Also a very expensive technology	Restricted reservoir volumes for higher volumes Expensive consumables that can typically not be re-used
Sample Transfer	✓	✓	✗	✗	✓	✗
Mixing	✓	✓	✗	✗	✗	✗
Bulk dispensing	Possible but limited and may require use of a less accurate multi-dispense mode and may increase risk of cross contamination Multiple re-fills of tip often needed	Possible but limited and may require use of a less accurate multi-dispense mode and may increase risk of cross contamination Multiple re-fills of tip often needed	✓	✓	Limited to low volume reagent dispensing and not really what it is designed for	✓
Typical volume range	2uL to 1000uL. Many manufacturers claim as low as 0.5uL but this requires very careful set up	25nL to 10uL in current automated platforms. Manual positive displacement pipettes go to higher volumes up to about 1000uL typically	0.5uL to 2500uL typical	50nL to 5mL	2.5nL to 5uL	10pL to 10uL

Support for your applications

When you first purchase an automated liquid handling system, lab service providers will allocate an engineer to help you set up the instrument and make sure everything is working from a technical standpoint.

When it comes to applications and running software on the instrument, you should consider whether you need assistance from a Field Application Scientist (FAS). SPT Labtech, for example, dedicates an FAS to each customer project. The FAS is responsible for pre-demonstrations which allow you to jointly create a customised plan for your demo in order to get an accurate preview of how products will improve your laboratory's workflows. The FAS then carries out the demo and runs a spotting experiment with colour dyes for visualisation so you can see the features and how it works. The FAS then does a post-demo discussion of results, designed to acquire initial feedback within your laboratory's set up. Based on the obtained result, the FAS is able to provide guidance on protocol adjustments to further improve the yield and quality of results. They will also be involved in ongoing training for lab staff using the instrument.

"FASs help scientists overcome challenges by sharing best practices to speed up new method implementation, reduce time required for new assay implementation and make the transition from full volume to miniaturized reaction set up simple".

Dr. Kamila Koprowska, European Field Applications Scientist, SPT Labtech



Questions to ask during the buying process with a lab service provider

There is no doubt that you'll have many questions when going through the process of purchasing an automated liquid handling system. To ensure you go home with the system most suited to your needs, bear these questions in mind when liaising with lab service providers.

- What kind(s) of dispensing technology is used?
- What's the optimum throughput level?
- Is plate handling automatable?
- Can it accommodate magnetic or plastic bead-based assays?
- What is the volume range, and how many different sample vessel types may be used?
- What is the flow rate spectrum?
- What is the precision %?
- What assay validation data is available for the specific liquid handler?
- How involved do you have to be day to day?
- Does it require a super-user or any user? Does it allow for pre-programmed and custom protocols?
- How do you maintain quality assurance of the system over time?

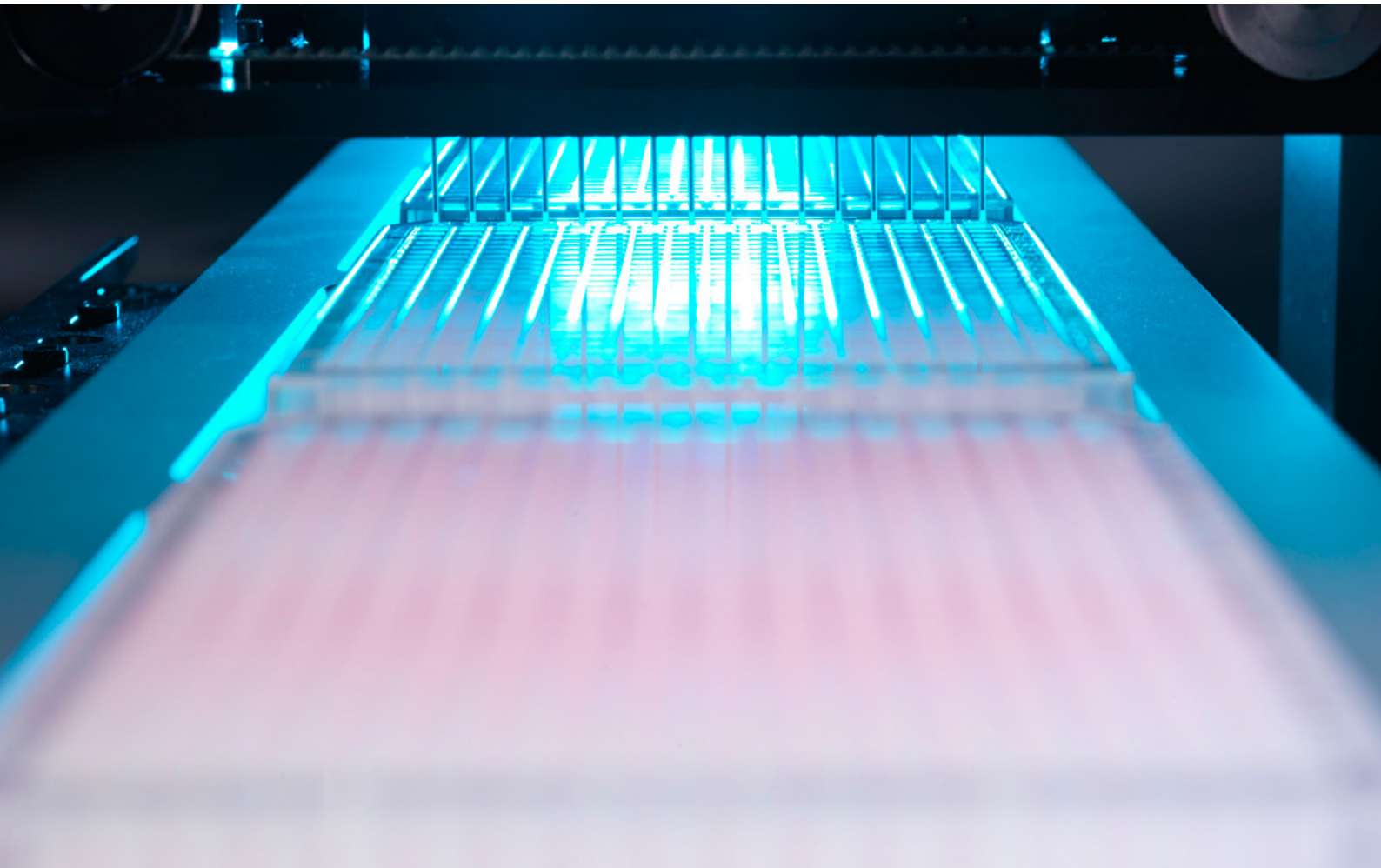
Key takeaways

This guide has highlighted how to build a business case for automated liquid handling and the factors you should consider when buying a handler.

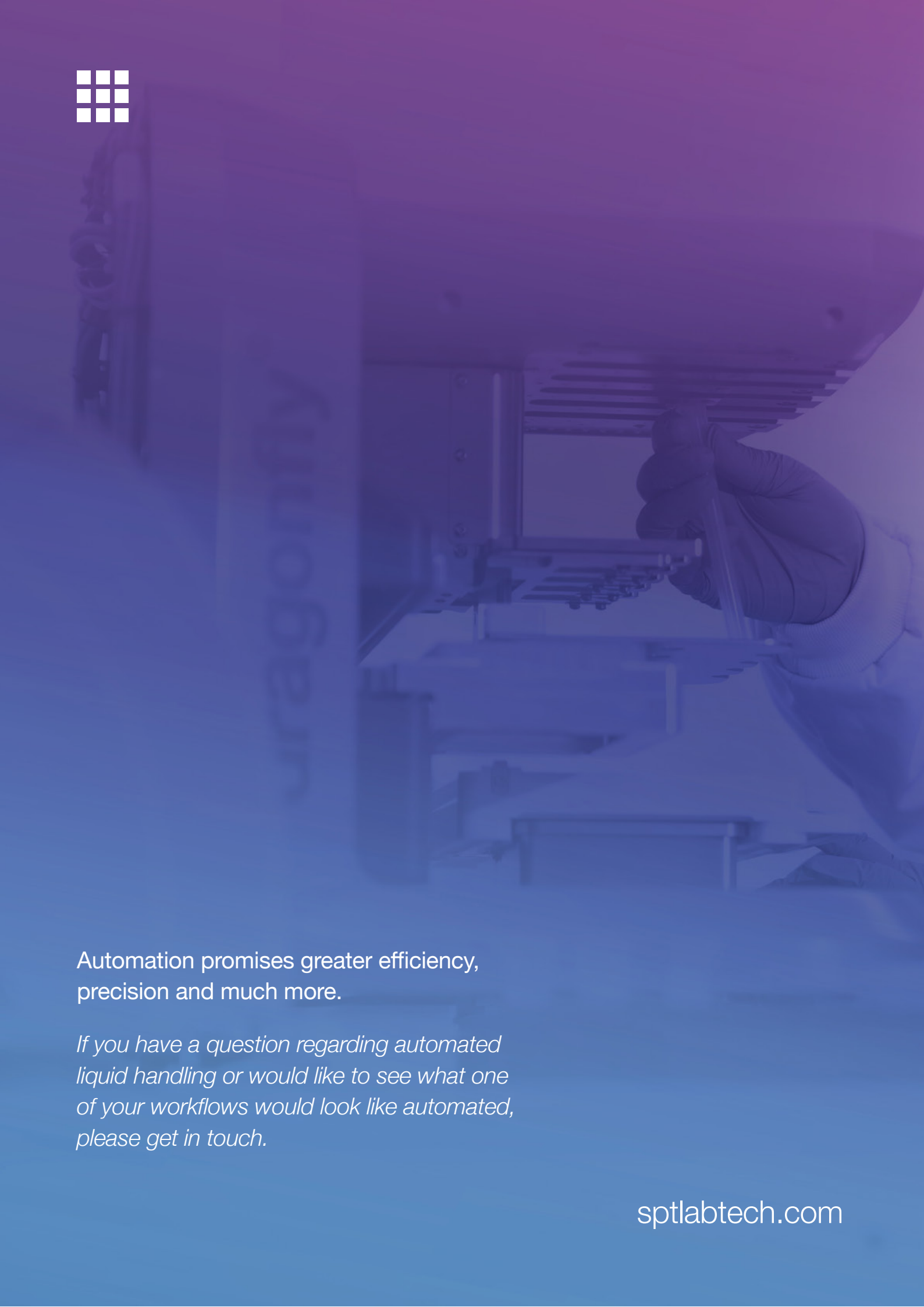
Let's recap these considerations to ensure the process is as seamless as possible.

- Start by building a business case for automation—what are you trying to achieve and what do you wish to automate? Identify the problem areas in your workflow and see if it's a good candidate for automation.
- Volume, throughput and liquid types - how much liquid do you want to move and how fast? Once you've determined this criteria, you'll be able to make an informed decision on which instrument will do the job.
- Which class of instrument will you choose?
  - **a.** Single channel pipettor;
  - **b.** 96, 384, 1,536 fixed tip array head;
  - **c.** 8/16 channel head with pipette tips;
  - **d.** Bulk dispensers.
- Consider how much space the instrument will take up in the lab and how it will impact the daily lives of scientists.
- Investment - what are the upfront and ongoing costs for the equipment and consumables.
- Running applications and support - what is involved in getting your workflow to operate on the instrument. How easy will it be to run and amend as your lab needs evolve? What support will you need from the lab service provider when it comes to installation and ongoing training?

As you explore your options, use this guide to support your decision-making. Making the move to automated liquid handling does not need to be a difficult task, providing you consider all the necessary factors to build a comprehensive list of requirements to suit your lab's needs.







Automation promises greater efficiency, precision and much more.

If you have a question regarding automated liquid handling or would like to see what one of your workflows would look like automated, please get in touch.

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