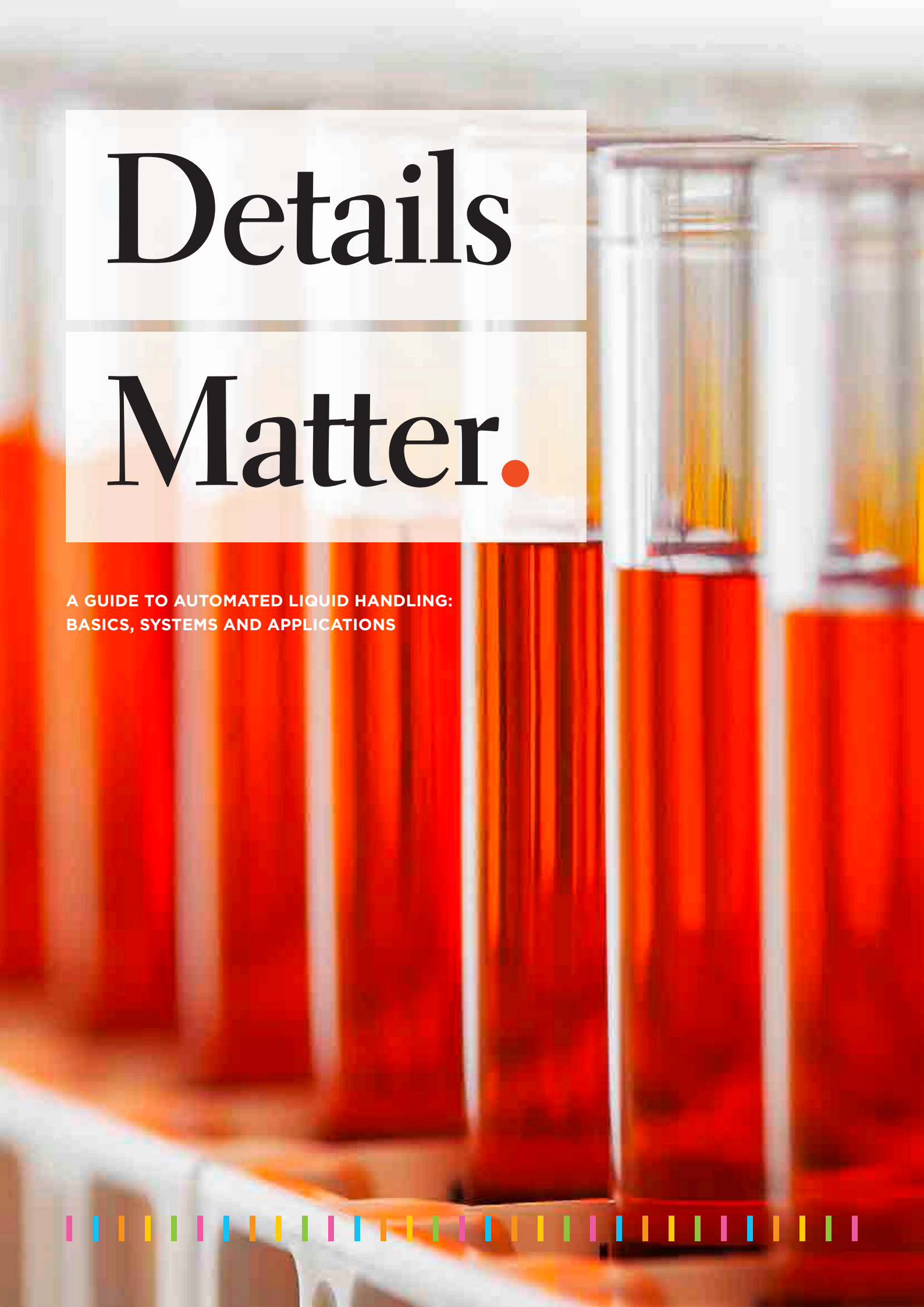

Details Matter.

A GUIDE TO AUTOMATED LIQUID HANDLING:
BASICS, SYSTEMS AND APPLICATIONS

Success is in the details.

If you are reading this guide, you are likely considering the purchase of an automated liquid handling system for your lab. Congratulations!

Whether you are automating a manual process or expanding an existing automated protocol, there are many details to consider and not all have equal importance for your final decision. The range of available choices today, from dispensing to detection modes and software tools, gives you the ability to finely tailor your system to meet the needs of your lab.

We have designed this guide to help you identify and evaluate in advance all of the details and choices involved in your purchase of an automated liquid handling system. Our experts provide key questions to consider during your decision-making process that will help ensure the success of your automation solution, both now and into the future.

Whether you are setting up a workstation for a single task like sample preparation or designing a system to perform a sophisticated, multistage workflow, your success lies in the details.

With your needs in mind, talk to Tecan. Where details matter.

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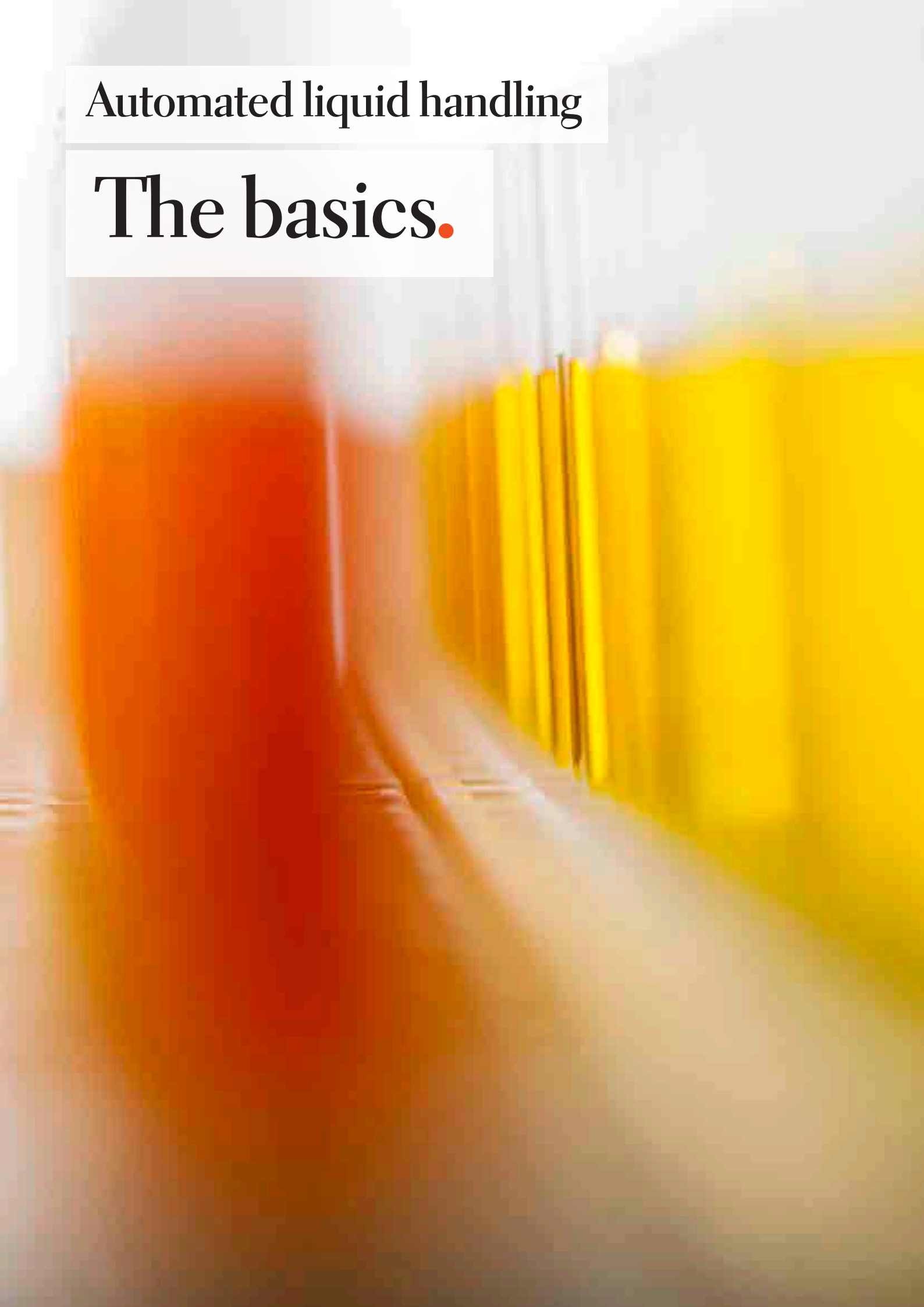
Automated liquid handling

The basics.



Automated liquid handling encompasses the use of instruments, software and control systems to move liquids, samples, plates and tubes from one place to another. It can include integrating peripheral devices such as shakers, incubators, barcode readers, tube decappers, etc. into complex workflows.

Automation helps scientists:

- Do more in less time
- Run processes unattended (walkaway automation)
- Do more with smaller sample volumes
- Improve experimental reproducibility
- Reduce reagent consumption
- Increase accuracy and precision, reduce errors, and improve data quality

"The most common driver for automation is to achieve higher throughput."

The main goals of automation are greater accuracy and precision, higher throughput, and improved reproducibility than are possible with manual processing. Automation can greatly improve a manual workflow, but it cannot fix an assay that does not already work manually.

Are you starting with a robust process that you have successfully run manually?

Before trying to automate your process, make sure you have a successful, robust assay and that you fully understand how your process works. Breaking your workflow down into individual steps will help you select the elements you need for an efficient, integrated automation solution. Consider in advance how each step and the overall workflow might impact your process.

For example, taking an assay from a manually pipetted, tube-based format to an automated, higher density, plate-based workflow means that the samples and reagents will be on the deck for a much longer period of time. How might this affect the integrity of your samples and reagents? Details matter.

Walkaway automation describes the ability of a system to run without manual supervision or intervention. The aim of allowing researchers to “walk away,” minimizing human intervention and letting robots do the tedious, manual and repetitive tasks offers important advantages: increased reliability, reduced costs, limited risk of human error, and more time for researchers to focus on designing experiments, interpreting data, and other important tasks. Building in automation carries an upfront cost, however, and it is wise to distinguish between what elements you consider essential and what it would be nice to have. You can readily design your system for one level of walkaway automation with built-in flexibility to increase it in the future.

"Walkaway automation is perhaps the biggest expectation among system buyers."

Needs change: What are the chances that your system will be used for a different purpose in a year or two?

Thinking only about your lab’s current needs may be short-sighted. Try to consider how your system might be used in the future. Liquid handling systems can easily be reconfigured as needs change. Many elements can be repurposed and upgraded. Build flexibility into your approach.

Is there an off-the-shelf solution to meet your needs?

Some smaller, specialized workstations have been optimized for specific applications with proven protocols, such as for DNA extraction, sample preparation, or cell culture. If a dedicated workstation meets your current needs, this could vastly simplify your selection process and still be a useful core component to integrate into a larger system in the future.

In today's lab environment, space is a precious commodity. Most liquid handling instruments are now multi-user, which has increased the demand for flexibility and innovative space design. Consider the possibility of adding automation that can access space below the bench. Floor-standing liquid handlers can access the benchtop as well as instruments or labware storage units below tabletop workstations, for example. You have many options: a benchtop or floor-standing liquid handler; a specialized workstation; or a modular system that can be readily reconfigured for different purposes. Whether you are considering an off-the-shelf or customized solution, do not overlook the issue of servicing and maintenance. Ease of access by technicians can reduce system downtime and disruptions to your workflow.

How much lab and bench space do you have, and are you using it efficiently?

Once you have purchased your automation system, it is time to get it up and running. Read on to learn more about developing and programming protocols and determining when and how to transfer your processes – whether being run manually or with some automated components – to your new automated workflow. With thoughtful planning you can make the transition efficiently, minimizing any loss of productivity.

Automated liquid handling

The building blocks.

Which basic building blocks of automated systems need to be your “must have” core components will depend on your goals and applications.

Pipetting

The most basic function of an automated liquid handing system is pipetting liquids. The key advantages are elimination of human error, greater precision and accuracy, and higher throughput. The two most common liquid handling technologies are liquid- and air-displacement. Each has advantages depending on the application.

"Pipetting is where automation eliminates a great deal of human error and accelerates processes."

METHOD	ADVANTAGES
Air displacement	• Ideal for dispensing small volumes (<5 µL) – decreased costs; reduced risk of contamination and incorrect results; increased speed and productivity • No extra steps required to move liquids or flush the system • Safer for handling radioactive or biohazardous materials • Compatible with fixed and disposable tips
Liquid displacement	• Works well with fixed-steel washable needles • Ideal if you require tube piercing or positive pressure pipetting • Compatible with disposable tips

A system that includes both air- and liquid-dispensing capabilities allows you to move easily between the two. Other small-volume techniques to consider for specific applications include digital and acoustic dispensing.

Volume ranges and labware formats.

What volumes and formats do you work with?

The automation system you choose must have the capabilities to handle the pipetting volumes and labware formats you work with, whether picoliter or milliliter volumes, tubes (up to 50 ml) or plates (up to 1,536 wells). Your vendor can present the advantages of automating each format. Now might be a good time to decide whether it would be advantageous to reduce from your current volume, either to save on reagent costs or to use less sample per assay and be able to extract more information from a single sample. Important considerations include how many plates/wells you want to run each day and what is your tolerance for precision.

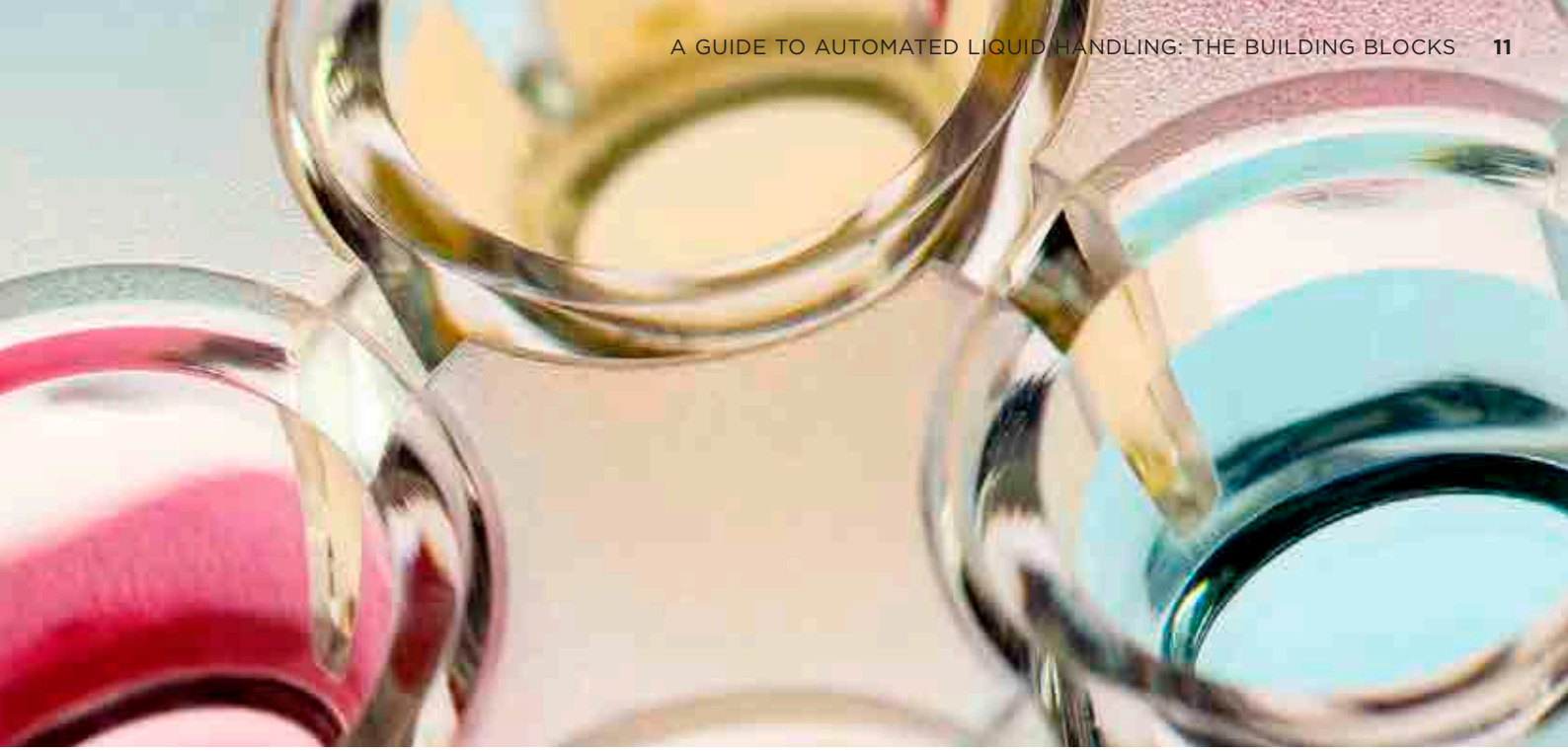
Pipetting arms

A range of pipetting arms is available to handle all dispensing requirements. The two main types are flexible pipetting channels (1 to 8) that can handle tubes, plates and many other labware formats; and multi-channel arms that are specifically designed for dispensing into plates, usually 96- or 384-well format.

For both types of pipetting arms, reservoir options are available to address all reagent requirements. Modern systems allow pipetting heads to be changed on-the-fly while processing samples. They are also compatible with a wide range of pipette tips, such as fixed needles, disposable tips or low-volume pin tools to support any workflow.

Pipette tips

Pipette tips may seem like a very small part of an automated system, but tip quality can make or break system performance and is a key contributor to reproducibility. You can choose from disposable or fixed tips. Some vendors now offer special low-volume tips validated for reliable dispensing at the microliter or sub-microliter levels needed for applications such as assay miniaturization.



Some vendors design their own pipette tips specifically to work with and optimize the performance of their pipettors. It is highly advisable to purchase original pipette tips to obtain the most reliable results.

Do vendors produce their own pipette tips, engineered to work with their instruments?

For many applications, it is now standard procedure to purchase sterile tips. However, if the product is labeled “pre-sterile,” this means that the product was sterile when it left the manufacturer, after which there are many opportunities for contamination. To minimize the risk of contamination, use only consumables that are labeled “sterile,” which means they are manufactured under sterile conditions and conform to packaging and transport standards that ensure tip sterility.

"Robotic arms can switch their fingers on-the-fly to ensure the best grip."

Robotic arms

Robotic gripper arms move labware around the automation deck. They can grab hold of a variety of tubes, microtiter plates and lids, disposable tip racks and other labware. Robotic arms can switch their “fingers,” sometimes on-the-fly, to ensure the best grip to pick up tubes or plates.

Core components.

Can the peripheral devices you need be integrated by your automation vendor?

Integrated Components

A broad range of peripheral devices can be integrated into your automated system, including carousels, plate washers, shakers, incubators, barcode scanners, dispensers and a variety of storage elements. These devices can sit on the benchtop or under the worktable and robotic gripper arms can move samples or reagents into or out of them according to process protocols. Experienced vendors will usually be technology-agnostic, but if you have not yet purchased your peripheral devices, make sure in advance that integration will not be an issue.

Plate readers

Although many plate readers can operate in a standalone fashion, integration in an automated workflow can yield increases in overall productivity. Many options are available to meet your lab's needs, such as readers with single or multiple detection modes, including absorbance, fluorescence, luminescence, and time-resolved fluorescence (TRF). Some readers also provide incubation capability, reagent injection temperature control (heating and cooling), gas control and lid handling. Key functions may include cell counting, confluence measurement and cell imaging.

"Integrating plate readers within an automated system can greatly increase productivity."

Is your assay temperature-sensitive?

Variations in temperature can impact measured signals and the quality of data. Too often temperature control during detection is overlooked. More advanced plate readers offer a cooling module that maintains the temperature within a narrow range for processes that are temperature-sensitive. This can improve the reliability of your results and reduce the need to repeat experiments.

Cell-based assays in particular depend on reliable temperature control throughout the experiment to maintain cell health. Even minor variations from physiological temperatures can induce heat- or cold-shock that can negatively affect cells, triggering stress responses and changes in cell proliferation rates, signaling pathways, and a range of unexpected behaviors including how the cells interact to external stimuli.

Software and sample tracking.

Software

Start thinking about your software needs early in the buying process. The hardware and robotics are certainly critical, but it is the software that can make a big difference in how you are able to program your system and tailor it to meet your needs. The distinctions in software from different vendors make it essential to discuss software capabilities when you consider different options.

> "Software is an area where there are clear distinctions between vendors."

System software is at the heart of any automated liquid handling platform. It controls the setting of process parameters, workflow, and data capture. Software design will determine the ease of programming and interaction with the system, and how much training you and your staff will need. Unless you have a software technician in-house, software ease-of-use can have a direct impact on your productivity.

Complex software may lead you to depend on the vendor or an external specialist to tailor programs, make changes and troubleshoot the system. You may need to wait for the availability of external consultants, putting your project timelines at risk. In many labs, the system operator is not likely to be a programming expert, and most IT teams do not get directly involved with instrument control software.

Questions you should consider:

- Does your vendor have a library of existing protocols to facilitate programming?
- What are the software integration capabilities of third-party devices?
- Ask the vendor about their device driver library and existing capability
- What is their experience with LIMS interfacing?
- Would you be comfortable programming the system yourself?
- Can you take the system software on a “test drive?”
- How easy is it for operators to set up their runs without programming expertise?
- What features do you need, like customizable graphical loading guides, and are they available?

Sample tracking

Barcoding can reduce errors in automated systems by making it easier to track samples and components. Automated labeling systems take up little space and have a short return on investment (ROI) time as they greatly improve productivity. An automated labeler can reach a throughput of about 400 tubes/hour and can pre-label tubes or label them in real time.

Automation of labeling and tracking may include individual tubes, vials and plates, can indicate location points on the deck and in storage units, and offers many other benefits:

- Ensuring that barcode labels are applied properly and can be read correctly
- Accelerating barcode reading and sample picking processes
- Streamlining integration of lab information management systems (LIMS)

Maintenance and compliance.

Would you like to see easy "undo" and "start/stop" buttons on your system?

Many automation systems cannot accommodate start/stop or undo functions, meaning that you might have to restart a program if you enter something incorrectly or need to pause a process midstream. Check if the control software has an error recovery feature; with smart automation the system should be able to detect, understand, report and recover from an error. If an operator needs to interact with the work area of an instrument during an automated run, start/stop functionality makes this easy and safe.

"Regular preventive maintenance minimizes instrument downtime and can increase performance."

What quality and reliability measures should you consider?

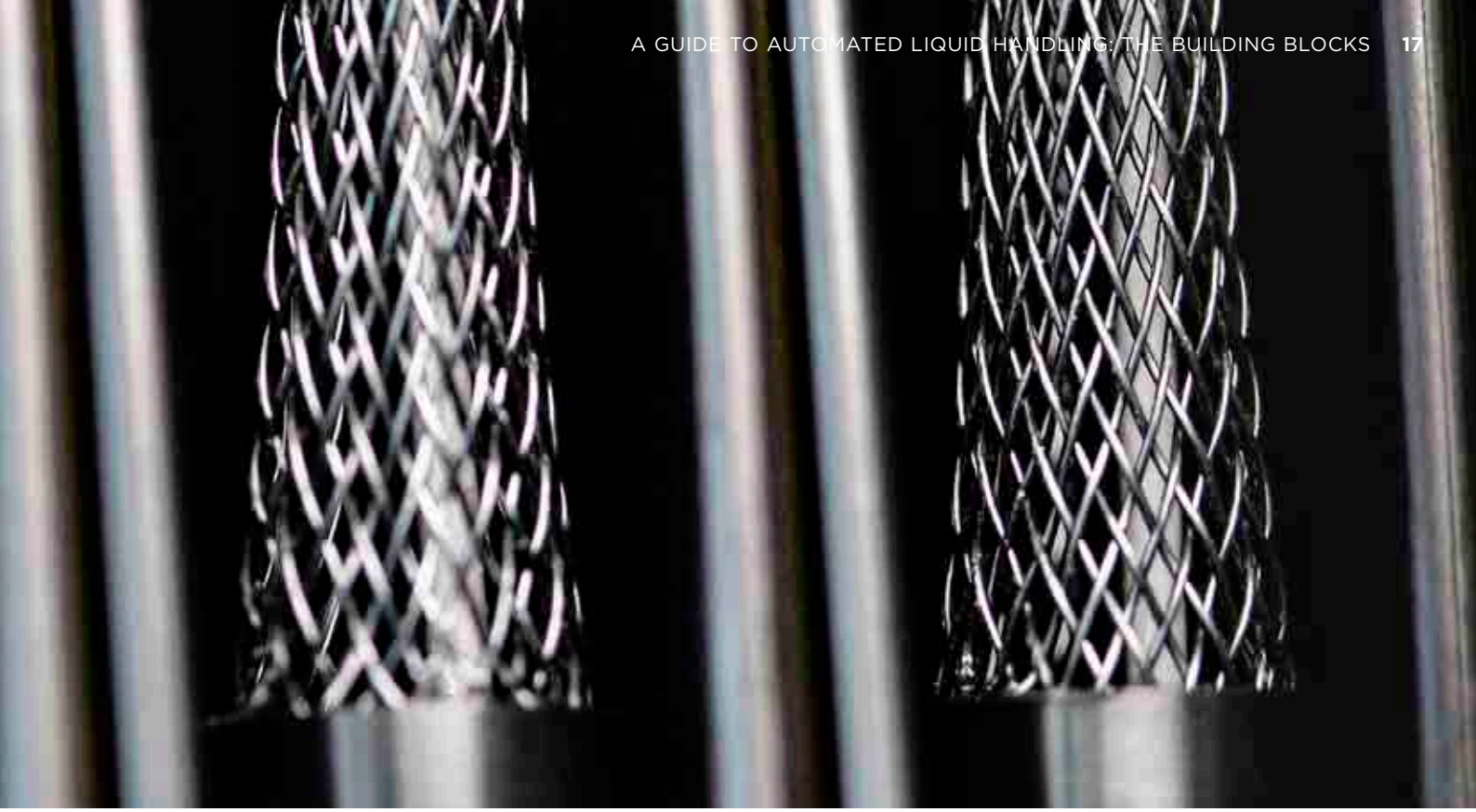
System maintenance

Regular preventive maintenance helps to ensure the accuracy and precision of your system and minimizes instrument downtime. Regular maintenance can also increase instrument performance and lifetime. A reliable system that requires minimal maintenance and rarely breaks down will have the least impact on lab productivity. Ask vendors for "mean-time between failures" data and take a close look at the recommended maintenance procedures for a system. Is it clear what you need to do and when?

How can you best set up a system in a regulated environment?

QC and regulatory compliance

For an automated system, quality control defines the accuracy and precision of liquid delivery. In regulated environments, you may need to prove the validity of your data at any time and your system should allow you to run a validation protocol with as little effort as possible. A robust liquid handling QC program will build quality into your processes and decrease costs by improving data quality and shortening timelines.



Become familiar with the full scope of regulatory requirements that affect your lab, such as GMP, GLP, ISO and 21CFR Part 11. In 21CFR Part 11 environments that require audit trails and the demonstrated ability to set access and control permissions with different user roles, ensure that these are features of the system software.

Consider your lab's regulatory compliance requirements, such as:

- Liquid handling capabilities with the option of sophisticated liquid-level detection and clot/clog detection
- GMP- or GLP-compliance that entails validation of the quality of your instruments and processes, and documentation for your IQ, OQ and PQ procedures
- Periodic QC runs to demonstrate that every pipette tip is dispensing the exact intended volume squarely into the plate well
- Conformation to ISO standards
- Safety certification to meet standards for UL, CSA and/or CE

Regular testing and validation of liquid handling instruments is one of the most effective ways to ensure reliable data. Select a system with software that tracks a preventive maintenance schedule and provides reminders. Some vendors offer certificates to your staff who complete simple QC training requirements.

Training, service and safety.

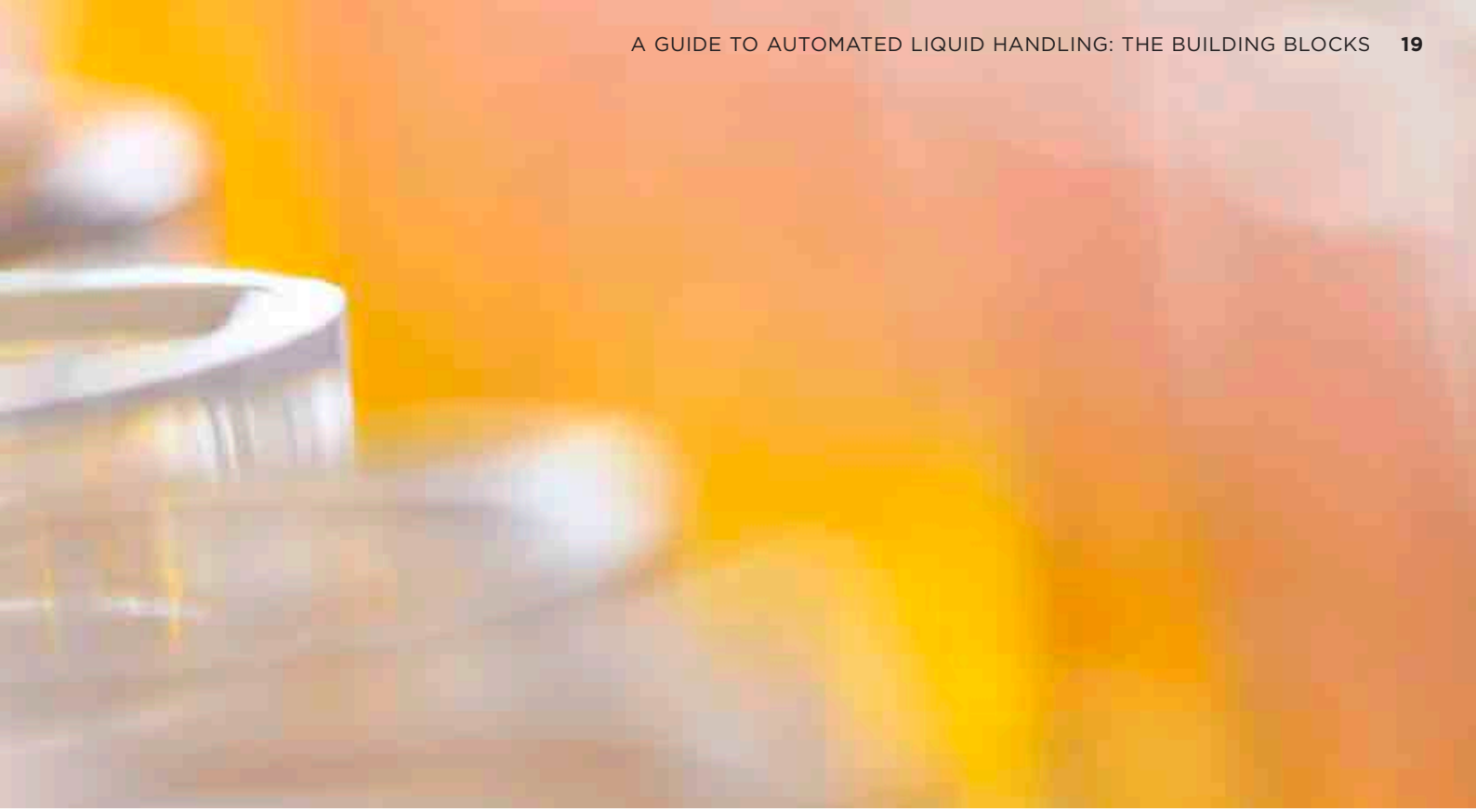
Training

Regardless of how easy it is to use an automated platform, staff training is instrumental for getting the most out of your system and maintaining it in optimal working condition. Being able to address staff turnover in your lab is also important. Therefore, discuss specific training needs with your vendor in advance, and make sure that training sessions are regularly available.

Coordinate the logistics of training before the system is installed so that you can get up and running quickly:

- How many staff will need training?
- Will training take place at your facility or at the vendor's?
- How long will training take?

"Service and regular maintenance are key to keeping your system running optimally."



Service

To keep your system running optimally, regular maintenance and service are key. Ask vendors about:

- Service locations and call-out time
- The qualifications of their service staff
- How many service technicians the vendor has locally
- Whether you might have the same technician over time to ensure continuity

Carefully evaluate service contract options and costs. Do not overlook the value of phone and online support.

How can I best protect my staff and samples?

Safety

Safety considerations and possible safeguards should include:

- Safety relative to the moving parts of the system – can the system be easily stopped if there is a problem?
- If you are operating in a biosafety environment or using hazardous substances, what can be done to protect the operator and the lab environment?
- Can the instrument or system be used in a laminar or HEPA hood to protect the samples if needed?

Key applications for automation.

The benefits of automation are especially relevant for certain key application areas and processes — such as genomics, cell biology, drug discovery, protein purification and characterization — and for meeting specific research needs.

Liquid handling technology can automate a wide range of tasks that may be tedious, complex, or error-prone if performed manually. Automation can also dramatically improve the precision, accuracy, speed, and reproducibility of a variety of commonplace protocols carried out in research and drug discovery labs.

Liquid handling technology has been applied successfully to automate a variety of workflows, including but not limited to sample preparation for PCR or mass spectrometry, DNA extraction for subsequent analysis such as next-gen sequencing (NGS), and performing cell-based assays or ELISAs for drug screening.

Genomics.

Genomics has seen explosive growth in recent years, as the cost of sequencing has decreased significantly, fueling the possibility of discovering biomarkers that may serve as targets for diagnostics and therapeutics development. Automation of whole genome and targeted sequencing approaches brings greater speed, precision, cost-savings, and productivity gains to genomics-based research.

"Automation adds speed, precision, cost-savings and dramatic productivity gains to genomics research."

DNA extraction

Both CLIA and research labs spend a lot of time and effort extracting and purifying DNA and RNA from samples. In recent years, a new less invasive technique has taken hold – cell-free DNA capture from plasma.

DNA extraction systems rely on bead- or vacuum-based techniques. Determining which method will work best for your objectives is a good starting point. Ask vendors if they work with chemistry kit manufacturers and whether they have ready-to-use validated protocols for those kits. This can save considerable time and costs due to shorter installation time and faster technical support. If you already know what extraction method and chemistry you want to use, explore how these can be automated.

Ask about:

- Proof data
- Software tools, their ease-of-use, and if they are customizable
- The availability of verified protocols
- Scalability of the system

Can I also automate DNA quantification and normalization?

Once DNA has been extracted from a sample, quantification and normalization steps can also be successfully automated. The system software and seamless integration of devices such as a microplate reader make this possible. They can save time, reduce steps and, when coupled with sample tracking, increase downstream accuracy and even identify samples that have a too-low or too-high DNA concentration for subsequent processing. Several vendors offer readers engineered specifically for DNA analysis.

PCR setup

Setup for PCR, qPCR and microarrays is often automated to reduce the risk of sample mix-ups, cross-contamination and user-to-user variability. The need to pipette small volumes with high precision and accuracy are key considerations, and instruments may vary greatly in these capabilities. Request documented specifications from vendors and look for systems with reliable sample tracking and an intuitive user interface.

NGS sample prep

NGS is now so common in research and clinical labs that some vendors have designed dedicated automated systems for performing sample prep, which is a crucial factor for achieving better study results. You will benefit most from systems that have a range of built-in protocols that have been optimized, tested, and the subsequent sequencing verified. The ability to integrate quantitation and normalization steps with automated NGS sample prep will increase your walkaway time.

Cell biology.

The use of cells and cell-based assays to study disease and develop therapeutics requires working with living cells, which can be tedious and time-consuming.

"Automation increases walkaway time and standardizes processes to increase reproducibility."

In a cell biology lab, automation can not only increase walkaway time, but importantly, it can also help to standardize processes and allow you to achieve more reproducible results. Automating tasks such as feeding and plating cells replaces manual labor with walkaway time — including in the evenings and on weekends — and improves standardization and reproducibility.

Cell culture

The health of your cells affects all downstream work, whether you are working with primary cells, stem cells, or iPCs. Your cells and processes will benefit from:

- The ability to reduce the speed of the robotic arm
- Use of large-bore tips suitable for cell culture formats
- Maintaining a sterile environment and minimizing the time cells are out of the incubator
- Incubation capabilities integrated into the automated system
- The potential to work in a protective environment under a HEPA hood

Cells can be particularly sensitive to changes in temperature and humidity. Advanced detection systems that include temperature and humidity controls within the reader and automatic lid-lifting features can help reduce temperature fluctuations, evaporation, and the risk of contamination.

Growing interest in 3D cell culture to more closely mimic the natural environment of cells and tissues greatly increases the complexity of cell culture compared to conventional 2D methods. 3D approaches may use a scaffold-based or gravity-based scaffold-free method, and automating either method can be quite challenging. Some vendors will have had more experience than others in automating different types of 3D cell culture techniques.

Cell-based assays

Cell-based assays allow researchers to study things like proliferation, kinetics, cytotoxicity, viability, and gene expression in live cells. The addition of substrates to the cells in these workflows is time-sensitive, and automation can ensure that dispensing occurs on schedule with enhanced reproducibility. Furthermore, cell-based assays often run overnight, and automation allows for processing without the need for lab personnel to be present.

Monitoring aspects of cell health such as proliferation, cell viability and apoptosis can provide significant biological insights. The introduction of multimodal microplate readers, which include cell imaging, has further expanded the range of capabilities for use in more complex applications like wound healing assessment and cell migration.

Drug discovery.

Due to the typical scale of operation, drug discovery depends on automated liquid handling systems to achieve efficient processing of large numbers of samples across the entire workflow. Drug discovery requires robust compound management solutions, unerring sample tracking, precise dispensing, and overall high throughput processes. Efficient integration and coordinated control of peripheral devices such as shakers, sealers, barcode printers and decappers are important.

Drug discovery begins with target identification and validation based on the investigation of molecular and cellular mechanisms associated with disease. Automation can add sensitivity and flexibility to the often challenging and time-consuming workflows required. If your processes are temperature-dependent, then temperature control in automated systems, particularly in your reader, is an important factor and can reduce data variability and improve experimental reproducibility.

When you are screening libraries of thousands or millions of compounds, sample tracking and accuracy are crucial factors across the workflow. To design an automated system that will best meet your needs, discuss throughput with vendors and consider the following points:

- Is your library in tubes or plates?
- Do you plan to do cherry-picking of samples?
- Does the system need to track samples?

If you are planning to incorporate phenotypic screening into your discovery program, what types of automation will deliver the most benefit depends on:

- How many cell-based assays you will typically run
- How many plates you want to screen
- How fast you want it all done

ADME/TOX screening to test for drug absorption, distribution, metabolism, excretion and toxicology is an essential part of drug discovery. Screening requires a range of different assay types including cell permeability, drug solubility, *in vitro* drug metabolism, protein-binding studies, compound characterization and cell-based assays. You can benefit from a scalable, versatile platform that meets your current demands and is flexible enough to meet your needs as they change in the future.

Can I work with tubes as well as 96-, 384- and 1,536-well plates?

Protein purification and characterization.

Proteins are increasingly a focus of attention as potential biomarkers, therapeutics and research tools. Scalable and automated plate-, tip- or column-based purification systems can generate large amounts of data to aid in scale-up. An experienced vendor can present the pros and cons of both plate- and column-based formats.

"Scalable, automated purification systems can help provide a precise forecast for scale-up."

Column-based separation approaches may closely resemble the chromatographic work you are already doing in your lab. Using specialized columns, you can miniaturize your separations protocols, automate them and run them in parallel to obtain more data more quickly. The complexity of protein purification protocols may require the integration of chromatography columns and media from multiple vendors as you develop an automated system. Here again, both hardware and software tools are critical. Ask the vendor for a software demonstration and if they have a wizard to help in setting up process parameters.

Mass spectrometry sample prep

Research, clinical and toxicology labs are performing ever-increasing numbers of mass spectrometry-based analyses and they are eager to address the major bottleneck in their workflows – manual sample preparation. A wide range of screening applications use mass spectrometry to identify and quantify unknown compounds in complex samples and confirm low-level trace components. The technique is widely used in food analysis, sports and workplace testing and biopharma research. It is also expanding into the clinical diagnostics and toxicology fields.

Appropriate sample preparation can improve your mass spectrometry analysis and reduce the wear-and-tear on the instrument caused by a simple dilute-and-shoot approach. Solid phase extraction (SPE), a sample cleanup technique commonly used to extract an analyte from a complex matrix, uses a column filled with a sorbent and liquid-liquid extraction with an immiscible fluid.

Can you reduce your mass spectrometry sample prep time and reduce errors?

Automation can accelerate mass spectrometry sample prep, improve your workflow and data quality, and increase throughput. It also reduces errors and the potential for exposure to hazardous materials. With today's intuitive, easy-to-use software even an untrained user can run these processes. Built-in functionality such as sample tracking make it easy to document chain of custody, even when working with large sample numbers.

Always there for you.

How long will it really take to get the system up and running with your workflow?
Finally your system has arrived! Before you begin developing protocols and programming the system, check with your vendor for pre-programmed protocols that are aligned with key reagent kit manufacturers.

System start-up and ROI may not be immediate. You will have to decide when and how to migrate to an automated workflow.

It's a big investment
The benefits of automation are significant and tangible, but be cautious not to overestimate the immediate impact, the timeline to full operation, or the prediction of ROI. Your vendor can help you prepare realistic forecasts and estimate the total cost of ownership (TCO).

Don't stop asking questions
When you have carefully reviewed your options, you will have chosen a leading vendor that has helped you through the process. By choosing to partner with an experienced vendor that has been involved in many more automation projects than you have, you will be able to take advantage of their expertise.

A good partner will be equally committed to your success today and in the future.

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Tecan – Who we are

Tecan (www.tecan.com) is a leading global provider of laboratory instruments and solutions in biopharma-ceuticals, forensics and clinical diagnostics. The company specializes in the development, production and distribution of automated workflow solutions for laboratories in the life sciences sector. Its clients include pharmaceutical and biotechnology companies, university research departments, forensic and diagnostic laboratories. As an original equipment manufacturer (OEM), Tecan is also a leader in developing and manufacturing OEM instruments and components that are then distributed by partner companies.

Founded in Switzerland in 1980, the company has manufacturing, research and development sites in both Europe and North America and maintains a sales and service network in 52 countries.

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