SECONDARY SCREENING WORKSTATIONS – the emergence of compact turnkey solutions that work!

With the launch of new workstations focused on secondary screening applications not only are we witnessing the shrinkage of laboratory automation but we are seeing the emergence of true walk-away solutions, ie set up the system, press start and go. This review highlights the advantages of these turnkey solutions in medium throughput screening and the opportunity it presents life science tool providers to package their screening technologies in a platform where the customer finally gets what they want, ie compact automation and validated data they can have confidence in.

By Dr John Comley

Until recently it was relatively easy to draw a clear distinction between screening done using a workstation or fully integrated robotic system. The term workstation has been variously defined[1,2] but most would regard it as an independent system that is highly specialised to perform a single function or task as efficiently as possible (eg a plate reader or liquid handling device). In a workstation (semi-automated) screening environment it is the human operator that moves the plates between workstations. In contrast, a fully integrated system has been defined[1] as a collection of instruments (such as those workstations described above), served by an articulated robot arm to move plates between these so-called peripheral devices. Fully integrated systems are usually controlled by scheduling software, which together perform all the steps of a screen from picking an assay plate to outputting screen data from a reader to a centralised database. So what has changed and why has the distinction between these two ways of performing the same basic processes become blurred? Quite simply, we are now beginning to witness the convergence of the workstation and the fully integrated robotic system into a much more compact integrated screening solution. The shrinking workstation was in fact predicted several years ago by Banks et al[1] who suggested that once workstations become more sophisticated and assay miniaturisation techniques more established, it will be possible to fit on a conventional bench a system that can perform all the steps necessary for an assay without tedious manual intervention. Clearly a significant driver has been the motivation to reduce the size of automated systems as laboratory space is at a premium. But we should not overlook the fact that most biologists appear to have a greater level of comfort with laboratory automation they can put on their own lab bench. Equally important is the shift in the bottleneck from HTS to secondary screening and assay development and the desire by these customers to obtain better quality, consistent data. However, the large life science tool providers are now getting behind this change as they see new opportunities to bundle their technologies together by selling fully validated and verified (out-of-the-box) applications, ie 'turnkey solutions that actually work'. The packaging of reagent applications with instrument platforms is not a new concept,

Table 1: Comparison of different approaches to assay automation

FEATURE	TRADITIONAL WORKSTATION	FULLY INTEGRATED ROBOTIC SYSTEM	TURNKEY WORKSTATION
System size	Typically benchtop	Dedicated room and services, fully enclosed robotic cell	Compact, small footprint, benchtop or custom table
Number of tasks performed	One, or specialised part of a process	Multiple and diverse, fully automated process	Several including reading, specific validated processes, walk away automation
Walk away plate processing capability	<100 plates	<1,000 plates	< 250 plates
Plate movement	From manually loaded stacker	Fully articulated robot arm, usually on a track	Typically plate gripper or plate mover, limited axis pick & place robot or instrument specific mechanism
Scheduling software	None	Essential	Partial requirement
Task/application complexity	Specialised component	Less specialised, but greater diversity	Specialised and/or fully optimised
Staffing resource	Minimal, supervisor	Several dedicated	Key user(s)
Staff training needed	Moderate	Extensive	Moderate
Vendor supported applications optimised to instrument	One aspect of application only	Partially supported	Fully, with significant gains in precision, reproducibility & throughput
Source of components/ system integration	Single supplier	Multiple suppliers/typically made to customer order by third party integrator	Single supplier/emphasis on single supplier integrated solution
Promotes new technologies	Partially	Limited, expensive to reconfigure, depends on upgrade of peripherals	Yes, but focus maybe limited by suppliers access to assay technology
Key strength	Task focus	Fully automated, better suite to larger screening campaigns	Pre-validated applications, enhanced processing speed, better service
Main area of use	Batch processing, typically plate reading or sample preparation	High volume HTS and uHTS	Secondary screening, assay development, ADMET, medium throughput HTS
Ease of implementation/timeframe	Simple/immediate	Difficult/1-6 months to agree specification, 6-12 months from placing order	Simple to install/immediate, no need to develop interfaces, no application validation required
Redundancy enabled	Yes, multiple units typically purchased	No, usually one-of-a-kind purchase	Possible, several systems may now be afforded
Price range	$50K to $200k*	$500k to >$1,000k	$125k to $300k

** some specialised imaging workstations can cost up to $500,000*

and very compact turnkey analysers have been sold in clinical diagnostics for many years, although the majority of these systems are tube-based and the number of samples processed per day, are usually in the order of 100s rather than 1,000s. For microplate-based turnkey workstations there is precedence from the genomics area for its successful customer acceptance. Companies such as Qiagen have for sometime offered a wide variety of high throughput automated applications to streamline workflow and improve productivity for a variety of molecular biology applications. Previously for drug discovery applications there have been many attempts by reagent providers to demonstrate how their technologies could be used with third party liquid handling platforms and various co-promotions or application notes have resulted. Although such demonstrations assist customers to develop these or related applications, for the most part they weren't fully supported in the automated platform software. What is different today is that suppliers are thinking about automating the whole assay process, including the reading, and they are providing all the necessary components from one source (ie hardware, software, chemistry and in some cases even biology). The aim of this review is to draw attention to some of these new turnkey solutions and to discuss their capabilities and limitations.

In **Table 1** we contrast the traditional workstation and the fully integrated robotic system with this new breed of compact turnkey workstation and highlight the main differences and advantages between them.

Perhaps the best known and respected example of a multi-tasking workstation is the **Tecan** Genesis®, which was first introduced in 1994 with nearly 5,000 units placed worldwide. The open architecture of this workstation allows integration of a wide range of modules and options like readers, washer incubators, thermocyclers, SPE and magnetic bead separation. The heart of the Genesis Workstation is a Genesis robotic sample processor equipped with a liquid handling arm with four or eight tips; and a second Robotic Manipulator Arm (RoMa) arm with a five-point rotational robotic gripper to move microplates between positions, devices and storage. Flexibility and the desire to accommodate changing user needs are key drivers in the Genesis's continued development. A major new Genesis upgrade is the Freedom™ workstation, which now has the ability to incorporate three arms. Users can choose from among four different arms: 1) the liquid handling arm; 2) the RoMa; 3) a new pick and place arm designed for very fast tube handling; and 4) a new RoMa with extended Z range available with centric or eccentric RoMa grippers. Freedom is available in nine different arm configurations. The Freedom RoMa arm with extended Z drive enables it to access peripherals (eg Tecan's Ultra™ plate reader) positioned below the worktable. Maximising the use of available vertical space without extending to the footprint appears to be a common theme among workstation suppliers. Tecan has also added a plate stacker option that can be used to feed plates directly on to the Freedom bed. The stacker can support between one and four columns, each capable of holding 50 standard

Tecan Genesis® LabCD-ADMET™ system

Beckman Coulter Biomek® FX liquid handler

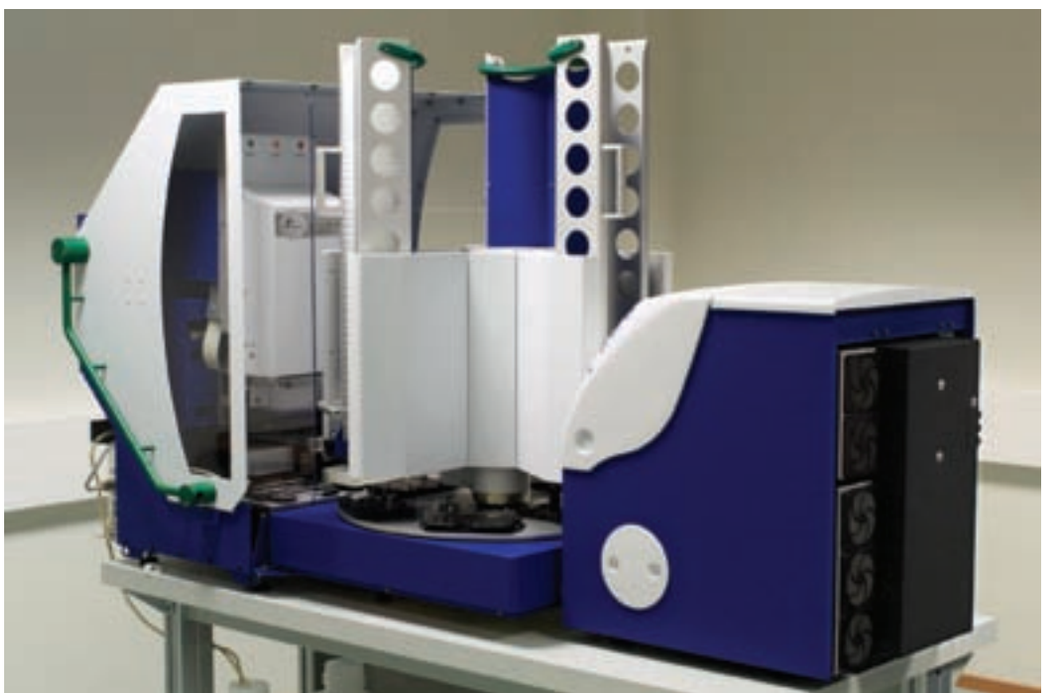
microplates. Other recent developments have included the TeMo multi-pipetting option, 96 and 384 heads, available with the new Impulse Technology (non-contact nanolitre volume) dispense head. Tecan has recently formed a reagents group based in Austria, and for the future we can expect to see more 'out of box' total solutions for various applications. Right now Tecan can provide specific instrument configurations and software scripts for third party reagent kits. It has further extended the capabilities of its Genesis 150 platform to create its turnkey LabCD-ADMET™ system, the first fully integrated, validated, miniaturised, 'industrial-strength' system for ADMET assays. The key attributes of the LabCD™ are that it can perform fluidic functions (unlike microplates); it integrates a wide range of assays types on a single disc; it enables assay miniaturisation (nanolitre volumes); it offers highly parallel processing with simultaneous initiation of assays; and it has sealed wells (ie no evaporation or meniscus effects). The LabCD utilises centrifugal forces to move liquids and spinning (rpm), capillary forces and design to gate samples through the CD, with on-disc microstructures providing on-board dilution and reagent distribution. Tecan makes reference to the simplicity and convenience of an automated and integrated CD format, how it provides standardised, high quality results and a complete walkaway solution. Tecan uses a modified version of its Ultra™ reader to control disc spinning protocols, incubation and reaction detection to provide either processed samples for further analysis or a complete chemistry assay using either: (i) standard absorbance, luminescence and fluorescence detection modes or (ii) bio-sensors. The resulting data from the Ultra can be processed, stored, manipulated and easily communicated to users using Tecan's Magellan™ data reduction software, giving the user information, not just data. Tecan currently offers two ADMET applications, a family of CYP 450 inhibition assays for measuring drug-drug interactions, and a family of serum binding assays for measuring the binding characteristics of drug compounds at various protein binding sites. Additional ADMET applications to be released in 2003 include Mdr1/PGP-ATPase (an assay for measuring potential interaction of compounds with P-glycoprotien) and UGT or UDP-glucuronosyltransferase activity (an assay for measuring glucoronidation of compounds in the presence of liver microsomes). Unlike other microfluidic systems Tecan has also addressed and patented the interface to the microplate world, ie the LabCD translates the microplate format directly into the circular format on the LabCD, using the eight channels of the Genesis pipetting head. It is important to note here that dispensing precision is not critical as it is the CD's microfluidics that meter volume. Throughput is currently not limited by transfer to the CD, but is dictated by the incubation time. Uniquely the CD actually supports long incubation assays as evaporation is not an issue within the CD. Although Tecan has demonstrated HTS assays on the LabCD down to about 100nL, it believes this is currently not a cost competitive application for the LabCD. This view might change once this 'full solution' achieves acceptance for ADMET and if 384 reaction CDs, with loading compatibility to the Tecan Impulse 384 head, become available.

The first application-specific CD format was launched by **Gyros** early in 2001, using Gyrolab Workstation as a flexible benchtop instrument platform that automates the processing of Gyrolab CDs. Almost every step from sample application to detection can be determined by Gyrolab Workstation Software. Application-specific methods control a high precision robotic arm that transfers samples and reagents from microplates or vials to the CD positioned on a spinning station, the speed of spinning generates the exact flow rate required for each step of the application. Gyros's first product offering, the Gyrolab MALDI SP1, is focused on sample prep for MALDI TOF mass spec. Protein digests are concentrated, desalted, mixed with matrix solutions and crystallised on MALDI target areas on the CD. The GyroLab Workstation simply transfers sample and reagent as required to the CD, all the volumes, processing and measurements occur within the CD microstructures. Gyros has proven a variety of

other applications in this technology concept including those of more interest to secondary screeners (eg enzyme assays, immunoassays and cell-based assays). Gyros's next product concept is to incorporate multiple microstructures each containing a miniature affinity column prepacked with affinity binders covalently coupled to beads in a CD microlaboratory. Within this CD format it will be possible to perform modified versions of well-established heterogeneous immunoassays in a sandwich format and customers could even bind their own chemistry. All the wash steps, processing and measurements (via laser-induced fluorescence as the CD rotates) would occur within the CD microstructures. Gyros believes this approach could give the user flexibility to tailor-make their own application CD as well as allowing them to benefit from parallel processing, using less reagents and sample etc. Specifically Gyros believes this concept would give users interested in protein array technologies the ability to quantify large numbers of proteins in a miniaturised and highly parallel format, by enabling the design of protein panels to suit their particular samples so they can examine protein binding, protein concentration and protein characteristics, eg post-translational modifications. From a secondary screening turnkey workstation perspective, Gyros should consider optimising a CD packed with streptavidin-coated beads as an automated platform for enabling a third party heterogenous immunoassay technology, such as PerkinElmer's DELFIA™, that to date has proved difficult to miniaturise owning to limitations in low volume microplate washing.

Beckman Coulter's workstation offering for secondary screening and ADMET is focused around its highly successful Biomek® FX liquid handler. Beckman Coulter has widely promoted this platform on the basis of: 1) flexible modular automation, with a variety of pipetting options and automated labware positioners (ALPs), providing task specificity for a wide variety of applications; and 2) rapid reconfiguration to accommodate virtually any change in your process with standardised, modular components that help you adapt efficiently. This approach has served it well so far, and the

PerkinElmer SmartStation™

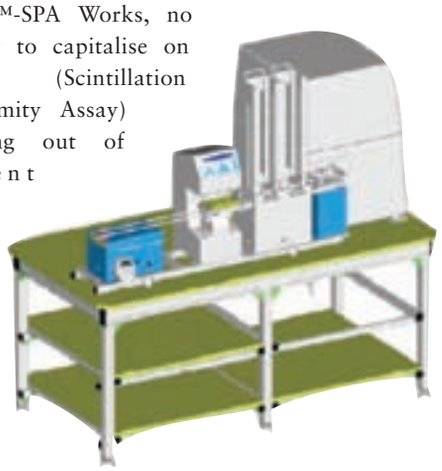


FX has rightly gained recognition as one of the market leaders in liquid handling workstations. But customers are demanding more, in that they now want to enable the whole assay process on the FX not just the liquid handling parts of an application. This is reflected in Beckman Coulter's latest strategy of providing 'smart solutions' for biological assay automation that combine hardware, software and chemistry together to provide verified applications and fully validated data in which its customers can have complete confidence. Workstation components currently include a variety of third party reader technologies, a Bio-Tek microplate washer and a unique reservoir ALP. A Kendro microplate hotel provides labware directly to the Biomek FX via a new shuttle ALP. However Beckman Coulter will significantly enhance its smart solution capability by the launch of its own reader ALPs that are being developed by its Austrian subsidiary (Anthos Labtec Instruments). These reader ALPs fit directly on the bed of FX, with the top of the reader box designed specifically as a plate processing surface. At present Beckman Coulter offers only a narrow range of reagents, currently limited to its Caspase 3/7 whole cell assay kits, but will soon include Caco-2 assay kits. However, these are only the first offerings in its New CellProbe HT Product Line and we can expect Beckman Coulter to be a major player in this market segment as it enables more 'out-of-the box' ADMET and even HTS screening applications. In addition, the capabilities of the Biomek FX platform will be further enhanced when Beckman Coulter launches its new 'A2 plate' microarray technology, that is composed of an array of arrays within the wells of a 96-microwell plate. The A2 plate allows for high throughput multiplexed profiling assays and utilises proprietary universal linker chemistry. A variety of biological molecules can be linked to generate custom arrays, although the initial focus will be on cytokine panels. The A2 plate will be adaptable to liquid handling automation on the Biomek FX and will include specific assay reagents and a dedicated A2 plate reader ALP. For the future Beckman Coulter believes it will be possible to shrink the size of the FX even further, making better use of vertical space and to increase the throughput (processing speed) to that currently possible on existing fully dedicated HTS robots. Beckman Coulter's new SAMI® Workstation Scheduling Software is tailored for ease of use on the Biomek FX. However, critical to future developments are adaptations to the SAMI software to allow for 'reactionary scheduling' and the ability to optimise the control of multiple dispense heads. Beckman Coulter's vision for the future FX extends beyond these improvements as it plans to provide information regarding the operation and status at each station in the system while that data is acquired. This will give the researcher the ability to proactively acquire quality control data on each step of the assay. When there is a question regarding a plate's data the researcher can

request the status information for each station the plate visited, at the time the plate stopped there. This provides confidence that the decisions made based on the data are correct and eliminate time and money of reprocessing questionable data. Beckman Coulter's main goal is to assist its clients in making the proper decision faster and cheaper.

PerkinElmer Life Sciences offers a range of robotic liquid handling workstations, including the CCS Packard PlateTrak, MiniTrak and Evolution P3 series. However, from a compact multi-tasking perspective their most innovative product is SmartStation™ which was recently launched at SBS Meeting in The Hague. SmartStation seamlessly integrates liquid handling, detection and plate management to provide turnkey automation, all within a very small benchtop footprint. PerkinElmer's EnVision multilabel plate reader provides SmartStation's detection capability. The liquid handling and walk-away rotary table and stacking unit in SmartStation originate from Wallac Oy and were previously part of the Fillwell workstation. Microplate transfers between dispenser, stacker and reader are exceptionally fast and smooth and occur via the rotary table. The dispensing unit features a 384 multichannel air-displacement dispense head which uses a proprietary disposable tip design that enables it to address 96- and 384- to 1536-well plate formats, without change of dispense head. The dispense unit also includes a novel compact reagent storage and refilling capability. SmartStation's Manager Software controls all workstation components, commands EnVision through protocols, enables limited event scheduling, utilises 3D autorecognition when configuring the system and allows for simulation runs. SmartStation's biggest advantage is that it has been developed for and will be comarketed with PerkinElmer's extensive range of reagent technologies including DELFIA®, LANCE™, [FP]2™ and its glow-type luminescence assays (Steadylite™ HTS and Britelite™). This means that customers can at last purchase fully optimised out-of-the-box applications which they can expect to work. The software features ready made assay wizards, which currently support DELFIA Eu-GTP binding assays and DELFIA ligand receptor assays. Wizards can be used as they are or opened and edited by the user. To illustrate how SmartStation has enhanced the performance of PerkinElmer's reagent technologies, its DELFIA Eu-GTP binding (filtration) assay has been successfully automated on the system. Previously DELFIA filtration assays were perceived as somewhat labour-intensive and throughput was severely limited by the lack of automated plate filtration systems that were reproducible and robust in terms of the effectiveness and uniformity of the vacuum filtration process and fast in terms of their plate processing capability. SmartStation's unique filtration system, mounted on its rotary table, addresses all these issues and represents a major advance in fast fully automated vacuum filtration. DELFIA has always been recognised a highly sensitive assay technology, now that the automation of filtration assays has been cracked all that limits its final acceptance as a legitimate high throughput technology is the availability of a suitable 384 filtration plate. While we wait for such 384 plates to emerge, users can immediately speed up 96-well filterplate assays by adding multiple filtration systems to the rotary table. SmartStation can process batches of up to 200 plates, has a throughput of about 60,000 samples dispenses per hour in 384, and a volume range of 0.5 to 300mL all within one dispense head. SmartStation is being targeted mainly at assay development, secondary screening and ADMET applications. One possible limitation of the current system is the lack of automated tip change and delidding, both of which may be addressed in future upgrades. PerkinElmer has the enviable position of offering a very broad range of reagent technologies, although its ability to leverage these reagents by successfully packaging them with its instrument platforms has been largely ineffective to date. Hopefully with SmartStation PerkinElmer will now be successful in enabling 'total screening solutions' where customer will derive immediate benefits in simplicity of set up through assay wizards and validated generic protocols, like DELFIA ligand receptor binding.

Not all companies with liquid handling and detection capabilities offer reagents, but this has not necessarily limited them from developing application specific workstations. For example **CyBio** has just developed the CyBi™-SPA Works, no doubt to capitalise on Spa (Scintillation Proximity Assay) coming out of patent



CyBio CyBi-Lumax 1536 S

Thermo CRS CataLyst Express

and the recent relaxation by **Amersham Biosciences** of the conditions under which its Spa beads are now sold. The CyBi-SPA Works combines CyBio's well known CyBi-Well pipettor with the CyBi-PlateSafe stacking module and its CyBi-Lumax 1536 S (an imaging intensifier based CCD image detector capable of single photon counting by means of special CyBi-Luminox optics) into a small, fast and reliable lead finding solution. Plate movement between devices is achieved using CyBio's standard plate slide with plates elevated on lifters through the plate slide. Owing to the bottom up reading mode of the Lumax detector the colour quench effect is reported to be negligible with settled Spa beads. However the broad sensitivity (380-650nm) of the Lumax detector means that is not limited to conventional SPA beads (that emit in the blue) but it also works well with the newer europium-based (LeadSeeker) beads (that emit in the red) and are less prone quench by coloured (particularly yellow) compounds. CyBio also offers the Lumax SD imager with fully integrated liquid handling from the CyBi-Drop dispenser (eight channels at 4.5mm spacing). This system is ideally suited for flash luminescent assays and has been fully optimised for the analysis of Ca2+ and GPCR activity via Aequorin-expressing cells. Dispensing occurs from the top of the plate with detection from the bottom. The flash-luminescent workstation requires its own table, because the camera is positioned below the surface of the table. CyBio's marketing slogan is that it provides scalable systems for automated lab solutions and in this respect the CyBi-workstations can be expanded into a more flexible system by integration of the CyBi-Tower short cycle incubator.

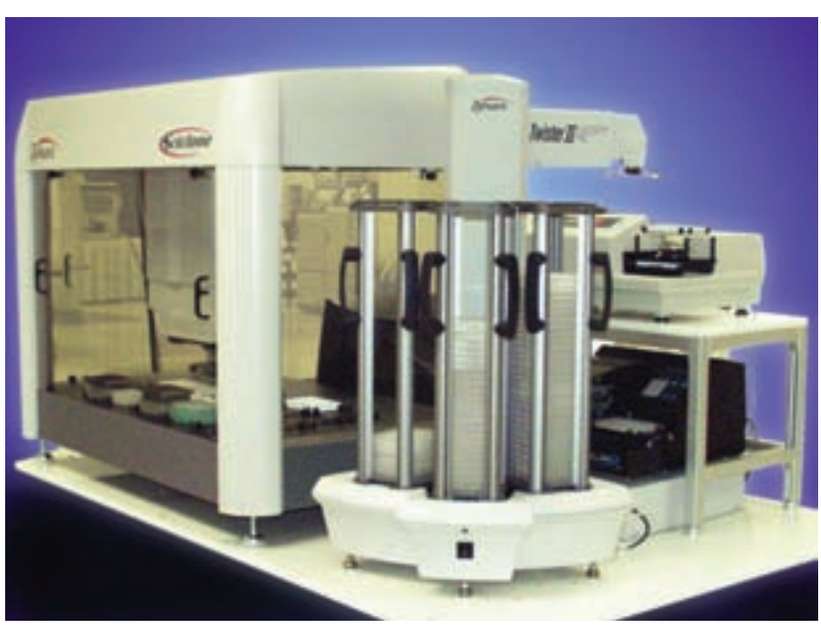
Thermo Labsystems which for many years appeared content to let others integrate its instruments has just launched its own family of workstations. Thermo Labsystems's new approach has been to take control of its tried and tested instruments (Multidrop 384 microplate dispenser, including its newly launched Multidrop Micro, Ascent (including Nepheloskan) microplate family of readers and Wellwash plate washers), none of which could be described as workstations as they all lack plate stacking capability, and integrate these devices together with a **Thermo CRS** CataLyst Express pick and place robotic arm to offer a number of so-called 'winning combinations'. All of these integrated solutions are now within a very small footprint. The CataLyst Express is Thermo CRS's CataLyst-5 microplate handling robot in a new benchtop configuration with random-access plate hotels that are easy to set up and teach. It is controlled using Thermo CRS's powerful POLARA™ method development and scheduling software. POLARA's multitasking capability enables the arm to continue functioning while the instrument is busy thus saving processing time. Thermo CRS's CataLyst Express, with its compact robotic arm can serve multiple instruments simultaneously, forming flexible systems for automation of plate handling in high and medium throughput environments. Thermo CRS and Thermo Labsystems now plan to leverage the undoubted benefits of these versatile and compact integrated 'combinations' by promoting them with its consumable products (eg Vitotox™ genetoxicity test kits, Luminometric reagents and kits; and its range of Microtiter® plates). This would seem a logical next step for Thermo Labsystems as it is already experienced in providing total solutions. Thermo Labsystems's Kingfisher™ 96 magnetic particle processor is just that: an instrument, optimised reagents, software, ready-made protocols, consumables and support; all designed to fully automate the time-consuming process of purifying DNA and RNA, proteins and cells from different starting materials in a 96-well plate format.

In direct contrast to other workstation providers discussed in the review, **Zymark** has made a concerted effort to avoid any dependence on a particular proprietary chemistry. Zymark prefers to focus on system reliability and flexibility, without locking its customers into unproven or proprietary chemistries or detection hardware. This leaves the

choice of assay up to the individual scientist, and allows for optimisation across a number of parameters – robustness, time, cost or automation efficiency depending on the particular needs of the pharmaceutical company. Zymark argues that automation should be flexible enough to offer room to grow with a company's ever-changing needs and to be adaptable to new assay chemistries and rapidly evolving liquid handling and detection technologies. Although these arguments hold true for HTS they are less important to secondary screening customers, who frequently want to run the same set of assays on a regular basis. Zymark has, however, recently placed a number of its highly compact Staccato™ systems for secondary screening applications. These systems are built around Zymark's Sciclone™ Pipetting Workstation at the core, but also have the ability to move plates on and off the deck (typically with a Twister™ II) and are usually interfaced with a variety of other automation to carry out specific applications eg third party plate washers, plate readers, and possibly a Zymark CO_2 incubator for cell-based assays. The Sciclone has functionality to do simultaneous 96-, 384- and 1536-well pipetting with cannula arrays or disposable tips from 50nL to 200uL, additionally the platform has an independent Z8 pipetting mechanism and up to six positions for bulk reagent dispensers. The Sciclone features a 20-position deck with a variety of accessories available that enable specific applications such as filtration, on-board shaking, etc. Zymark is currently launching the next version of the Sciclone platform called the Sciclone ALH 3000 – which will have added capabilities compared to the existing platform. The 3000 will allow the user to manually swap out the 100nL, low volume, and high volume dispense heads greatly improving the overall dynamic range of the platform. Additionally, Zymark has taken steps to improve the functionality of the Z8 pipettor and to improve the precision and low volume capabilities of its bulk reagents dispensers (now 500nL at better than 5%CV). Most importantly it has redesigned the software for the ALH platform to be much more user friendly. Staccato workstations are delivered complete with Zymark's CLARA™ easy to use integration Software. The CLARA Method Editor has the capabilities to easily create and modify assay sequences. CLARA's simulation mode allows you to optimise workstation operation without wasting samples. Zymark, like Beckman Coulter, shares a view for the future where monitoring technology will be extremely important in terms of regulatory validation. Users will need to be able to set up an audit trail and create log files in real time to monitor fluctuations within each automation module. Automation systems that can track such things as the time a plate came in under a liquid handler, the reagents that were added, and the exact incubation times will aid the researcher greatly in validating their science.

Summary

To summarise, the key benefits of turnkey workstations are listed in **Table 2**. From an end-user perspective the standardisation of assay technology, implicit in many of these systems, can be expected to yield real improvements in the quality of data generated, between assays and between global screening sites in big Pharma. In addition, since all the components come from a single source, customers can expect to have much greater confidence that the assays purchased will function reliably, as the supplier intended, and if problems do arise to see them resolved faster by a single system engineer, avoiding the issue of who is responsible, so often encountered in multi-vendor solutions. We can also expect the graphical user interface and associated software developed by these turnkey solution providers will be more instrument and application specific and to seamlessly promote smoother functioning of the entire process, including data manipulation, to that which might be obtained from a third party integrator who is less familiar with the application. However, there are downsides of purchasing a turnkey solution in that if you no longer need the application purchased you could be left with



Zymark Staccato™

Table 2

Key benefits of turnkey workstations

- Standardisation of assay technology
- Optimised streamlined process and application
- Increased speed, efficiency and throughput
- Increased productivity and reliability
- Improved reproducibility and assay precision
- Better validated and verified data
- Walk up and walk away automation
- Minimal user intervention and possibility for human error
- Very compact (typically benchtop) footprint
- Out-the-box solution, up and running immediately
- Simpler after sales support and service

References

1 Banks, M, Binnie, A and Fogarty S (1997). High Throughput Screening Using Fully Integrated Robotic Screening. J. Biomol. Screening. 2(3): 133-135.

2 Oldenburg, KR (1999). Automation Basics: Robotics vs. Workstations. J. Biomol. Screening. 4(2): 53-56.

expensive redundant hardware. However, most of the systems described in this review will still support user-developed applications within the limitations imposed by the onboard detection modalities. In fact, Tecan's LabCD Genesis has been specifically designed to enable conventional microplate-based processing, in addition to supporting the LabCD format. Other limitations in turnkey workstations relate to the limited plate stacking capacity of most systems, which may be less of an issue if higher density plates are supported. In addition, there has always been much debate regarding the benefits to throughput of putting a single reader online where the reading step is potentially rate limiting. These limitations ultimately impact on where such systems fit within the drug discovery process and it is unclear whether the unattended (walkway) throughput currently offered is sufficient for many HTS customers, despite the enhanced assay processing times that many of these new generation workstations will enable? The main niche being targeted by most suppliers appears to be the secondary screening arena, ie hits to leads, lead optimisation, profiling and ADMET, where throughput is currently less of an issue and to a certain extent the same assays are being run week after week.

New tube-based fully automated compound stores that are being implemented today were designed with a maximum cherry-picking capability approaching nearly 100,000 tubes per day. Screening of this number of data points per unattended run in 384 plates is not unthinkable on many of the turnkey workstations described in this review. We might therefore imagine that these new workstations could be used to enhance the process by which selected screening sets or focused libraries based around leads are screened and facilitate the decentralisation and distribution of that screening capability across drug discovery departments and sites. For example, it would be more cost-effective to duplicate many of these workstations globally than have a large centralised robotic system.

Finally, as a word of caution, turnkey workstation suppliers need to appreciate that a proportion of screeners are highly sceptical about 'out-of-the-box' assays, believing these to have been primarily optimised by the manufacturer to promote and maximise recurrent reagent sales. Although most screeners might be willing to go along with the supplier's recommendations for a 'one-off' assay, where cost and time to redevelop the assay would be a big issue, when it comes to running such assays as routine secondary screens many Pharma as a first step will want to pull that assay apart, to fully understand its limitations, it dependencies, its interferences and robustness, so that if something goes wrong they can directly and quickly troubleshoot. But their primary objective in reworking off-the-shelf protocols is to minimise reagents consumption, ie reduce assay costs per data point generated.

It remains to be seen how popular the smart turnkey workstations described in this review will prove with secondary screening customers as most of the products and applications mentioned are only just becoming available and some are still unproven in a screening environment. However, judging by the supplier focus on this market segment we can assume there is an unmet need in this area and systems of this type will impact on secondary screening over the coming years, particularly as more applications come on board. DDW

Dr John Comley *has more than 20 years' experience in Drug Discovery. He received his PhD at Imperial College, London University in 1978. After post-doctoral work at the University of Liverpool and the University of Vermont he joined the Wellcome Research Laboratories, Beckenham, UK in 1982. Following the merger of GlaxoWellcome in 1995 he worked in the Lead Discovery Unit at Stevenage. At GlaxoWellcome he pioneered investigations into uHTS (implementation of 1536 well technology). He joined PerkinElmer Life Sciences at Wallac Oy, Turku, Finland in 1999 as Manager HTS Technologies. He was responsible for the development of the Fillwell Liquid Handling Workstation and for the assessment of novel enabling HTS technologies. Dr Comley recently left PerkinElmer (February 2002) and is now an independent consultant, specialising in enabling technologies for Drug Discovery.*