BULK REAGENT DISPENSERS

ubiquitous liquid handling tool for microplate filling!

The initial success of the bulk reagent dispenser (BRD) as an automated liquid handling product can be attributed to its simplicity and low cost. Its current role as an essential dispensing tool in those labs requiring microplate filling and assay assembly has depended on its evolution to meet changing needs, particularly assay miniaturisation. Most of today's BRD systems now utilise some sort of solenoid valve, many are pressurised. Most are able to address the 96, 384 and 1536-well plates in the volume range 0.5µL and upwards. Flexibility to dispense multiple reagents is now a common feature, with individual addressable channels enabling any tip to dispense any volume into any well of a plate. Tip clogging, however, remains problematic, for which adequate solutions are only just beginning to emerge. Overall today's BRD are very much improved in terms of their capabilities, performance and software control over those obtainable 10 years ago. However, improved BRD reliability and robustness remains the biggest cause for concern, particularly among high throughput users. Time will tell if the BRDs discussed in this article adequately address these concerns and if true industrial standard reliability has now been achieved. One thing seems certain, BRDs will be needed by labs requiring fast plate filling for the foreseeable future.

By Dr John Comley

A bulk reagent dispenser (BRD) as the name implies is a liquid handling device that is able to add bulk reagents to the wells of a microplate. Typically BRDs have an 8, 12, 16 or even 24-channel head and liquid is dispensed into wells on a column by column basis, however dispensing on a row by row or even individual well basis is now possible on some instruments. On most BRDs you can define which rows you want reagent added to (ie you can deselect rows for control purposes), however, it is quite usual for all wells to receive the same reagent or solution containing cells. The first BRD developments were based on peristaltic pumps with a single reagent source (back-filled) from a common reservoir. Some instruments had a common manifold from which multiple dispense channels arose; in others the fluid path was separate for each channel, and

Figure 1: Main purpose or use of bulk reagent dispensers

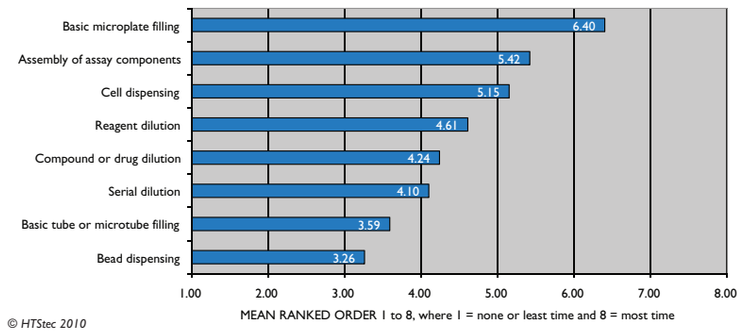


Figure 2: Main application areas where bulk dispensers are deployed

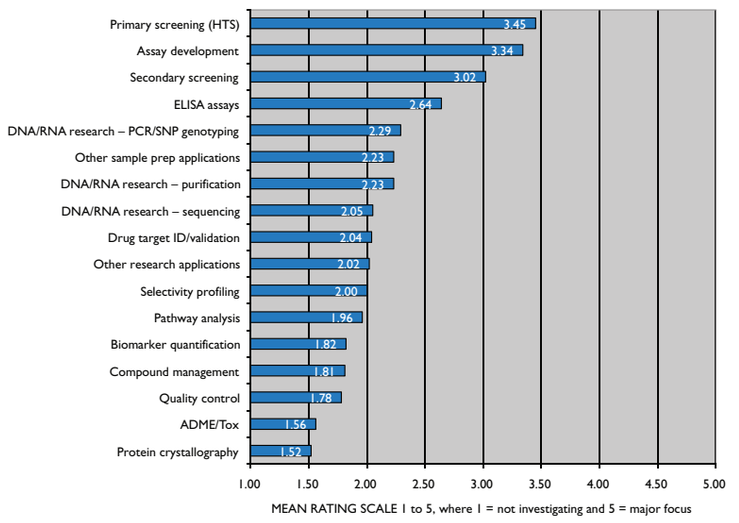
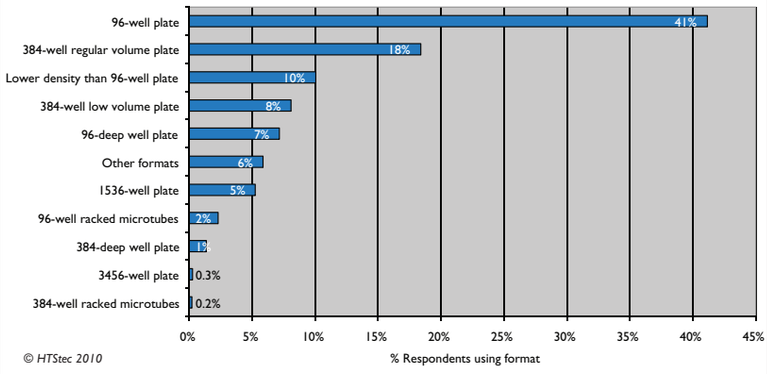


Figure 3: Percentage of bulk dispensing done in plate/racked tube formats



supplied as a disposable fluidic cassette. For the most part the first BRD instruments on the market were not able to dispense precisely (ie with a %CV of less than 10%) below 1-2µL. Assay miniaturisation, however, created a demand for lower volumes (<0.5µL dispensed per well) and with it BRDs evolved to use solenoid valves, initially pressurised by syringe pumps and more recently by pressurised bottles or containers. Quite a number of variants exist with respect to the type of valve used, the isolation of the pressurised loop and the use of tips or nozzles. What makes BRDs particularly useful is that they dispense liquid in a non-contact fashion (ie they use force to eject liquid from the dispensing element, and it does not involve contact with the destination plate) and the dispense head can move with great rapidity across the top of the plate, in some cases 'on-the-fly', in other versions dwelling, albeit briefly, over the well. However, what contributed most to the initial large scale deployment of BRDs was their low cost (typically <$10K for the peristaltic pump versions) and the relative simplicity of the instrument design. In terms of number of units sold, the BRD is the most successful automated liquid handler and has now become the mainstay of dispensing in those labs involved in plate filling and assay assembly. In this review we look a bit closer at how BRDs are used today, what aspects of dispensing are still problematic, and the impact perceived deficiencies have on purchasing decisions[1]. These observations provide the setting from which the latest BRD product developments are reviewed and we get a glimpse of how the BRD continues to evolve to meet changing user needs.

Current use of bulk reagent dispensers

Survey respondents had a median of two BRDs per lab, with around half of all instruments used today sourced from Thermo Fisher Scientific. Basic microplate filling was ranked the main purpose or use of their BR dispensing (irrespective of the application area). This was followed by assembly of assay components and then cell dispensing. Least time was spent bead dispensing (**Figure 1**). Primary screening (HTS) was rated as the main application area where BRDs are deployed. This was closely followed by assay development, then secondary screening and ELISA assays (**Figure 2**).

Sample formats dispensed

The majority (41%) of survey respondents BR dispensing today (2010) was done into 96-well plates, this was followed by 384-well regular volume plates (18%) and then lower density formats than

96-well plates (10%). Of the sample surveyed only 5% of BR dispensing today was done into 1536 plates (**Figure 3**). The main changes in BR dispensing formats over the coming few years are expected to be decreases in the use of 96-well plates and other formats, and increases in 384-well regular volume plates, 384-well low volume plates and 1536-well plates.

Liquids dispensed

The majority (48%) of survey respondents BR dispensing involves aqueous solutions. This was followed by media with cells (15% of BR dispensing); protein solutions (eg enzymes, receptors, BSA etc) (13% of BR dispensing); then DMSO solutions (7% of BR dispensing). Least BR dispensing (less than 2% for each) was done with high viscosity solutions (eg glycerol, sugars etc) and organics (eg ethanol solutions, scintillant etc) (**Figure 4**).

Volume ranges dispensed, batch sizes and throughput

The dispensing volumes ranges most used by survey respondents were: 50µL-500µL in 96-well plates; 5µL-50µL in 384-well regular volume plates; and 0.5µL-5µL in 1536-well plates (**Figure 5**). The median number of plates processed per batch when BR dispensing was: 5-10 plates for 96-well plates; 10-15 plates for 384-well regular volume plates; and 25-30 plates for 1536-well plates. The typical median throughput (number of plates processed per 8h day) recorded was similar to the batch size for 96-well plates (ie 5-10 plates/8h day); but was greater than the batch size as the plate densities increased, ie 15-20 plates/8h day for 384-well regular volume plates; 40-50 plates/day for 1536-well plates.

Dispensing reliability and problems

Around three-quarters of respondents surveyed were happy or generally satisfied that their existing BRD systems meet most of their current needs, and estimated the functional lifetime of their dispensers to be around five years. The median reliability of respondent's BRDs was, however, rated >90% fully operational, ie around 10% of all bulk dispensing time/work was disrupted due to instrument failures or dispensing problems. Of those problems tip clogging, particularly on small orifice devices, was ranked the most problematic aspect of BR dispensing today. This was closely followed by unsatisfactory retrieval of unused amounts of reagents (eg dead volume too high); then routine fluidics path clean-up and wash-out (eg takes too long, uses too much fluid); and need to continuously QC and recalibrate dispenser (Figure 6). Perhaps not surprisingly, survey respondents ranked good reliability and robustness as the device-related factor that was of greatest importance in a decision to purchase a BRD. This was

Figure 4: Percentage of bulk dispensing done using various liquid types

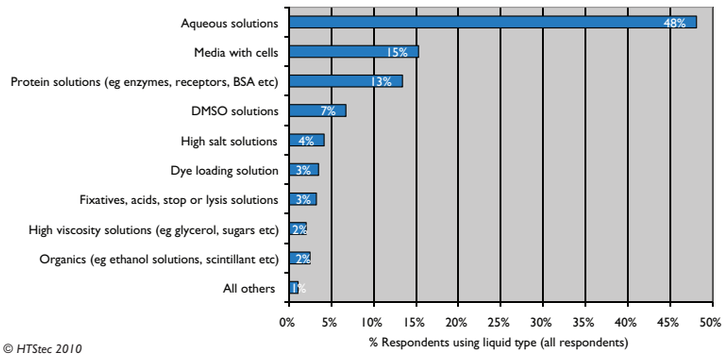


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Figure 5: Most used BRD volume range associated with formats dispensed

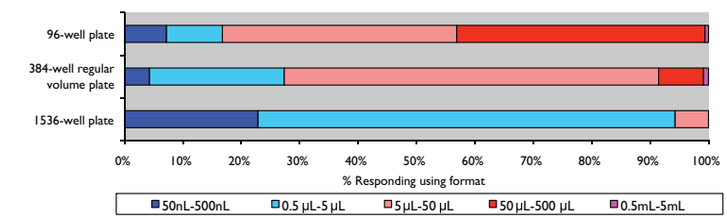

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Figure 6: Aspect of bulk reagent dispensing today that is most problematic

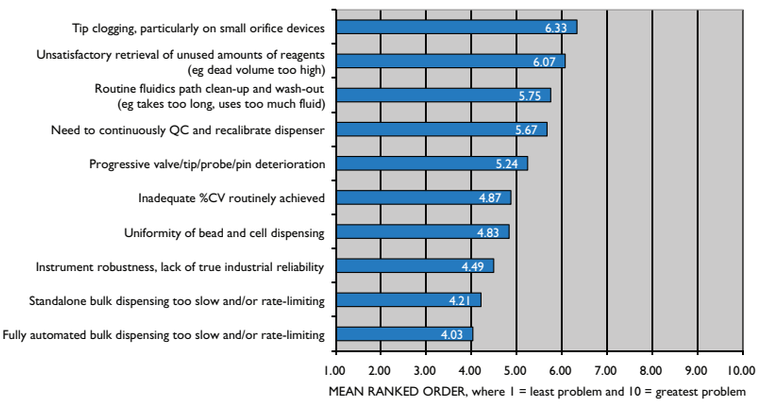

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Figure 7: Impact of device-related factors on BRD purchasing decision

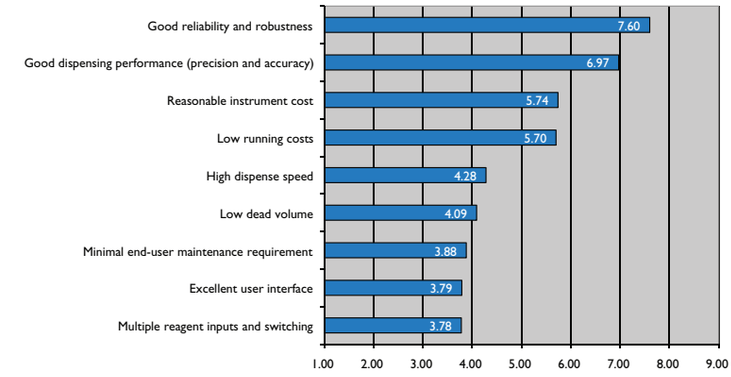

Figure 8
Beckman Coulter BioRAPTR FRD Microfluidic Workstation

Figure 9: BioTek MultiFlo™ Microplate Dispenser

closely followed by good dispensing performance (precision and accuracy), and then by reasonable instrument cost and low running costs. Other instrument-specific features, such as the dispensing speed, dead volume, multiple reagents inputs and switching, were ranked of much lesser importance compared to reliability and robustness (**Figure 7**).

Latest vendor offerings

The following snapshots provide details of the current status and recent progress vendors have made in the development of BRDs.

The BioRAPTR FRD Microfluidic Workstation from **Beckman Coulter** (www.beckman.com) is a high-speed, non-contact bulk reagent dispenser of up to eight reagents in one pass. The BioRAPTR can dispense all eight reagents into a 384-well microplate within one to two minutes or into a 1536-well microplate in less than five minutes. A new development for the BioRAPTR dispenser is the Automated Assay Optimisation (AAO) for BioRAPTR software for streamlined assay development and optimisation. Supporting 384- and 1536-well plates, AAO for BioRAPTR is designed to automate the dispensing operations of Design of Experiment (DOE). The software will import experimental design from statistical software packages, guide users to set up experiment parameters including non-reagent factors such as incubation time, generate randomised plate maps, and export a text file of deconvoluted results ready to be imported back to the statistical software. Helping execute the DOE with multiple factorial levels is the BioRAPTR dispenser's independent reagent control, allowing users to dispense a specified volume into any well for any of up to eight reagents at a time. Assay development such as media optimisation for protein production can be accomplished quickly and easily through AAO for BioRAPTR software. With the system's low heat, independent vertical fluid lines, and low system air pressure, the BioRAPTR dispenser is gentle enough to dispense cells without damaging their membranes. The BioRAPTR FRD dispenser has a volume range of 100nL to 60µL with excellent accuracy (< 5% CV), ideal for miniaturising high-throughput screening, PCR set up, cell-based assays, and more (**Figure 8**).

BioTek's (www.biotek.com) new MultiFlo™ Microplate Dispenser is the latest advancement in bulk dispensers offering up to four reagents dispensed in parallel with a choice of either peristaltic pump or microprocessor-controlled syringe drive technologies. A wide array of plate types are accommodated from 6- to 1536-well formats. The

MultiFlo dispenses a broad volume range from 1µL to 3mL accurately and precisely with a fully modular and upgradable design. BioTek's proprietary angled dispensing ensures compatibility with all dispense protocols including media exchanges with loosely adherent cell monolayers. With a compact footprint and base height of less than eight inches, the MultiFlo easily fits on any laboratory bench or robotic system. Together with a BioStack™ Microplate Stacker, up to 75 plates can be reliably dispensed by the MultiFlo with walkaway confidence (**Figure 9**).

With the ability to control individual channels over almost an infinite range of delivery parameters, the Synquad systems offered by **Digilab** (www.digilab-global.com) provide the user with the ability to accurately transfer via non-contact with target substrate µL to nL aliquots of sample with extreme precision regardless of viscosity. Novel features make it possible to deliver viable cell cultures previously only transferrable by tedious manual means. A second channel can then provide precision dosing thus insuring high throughput transfer for multiple drug evaluations. The Axsys software allows the units to be used in non-standard plate configurations and has been integrated into automated protein crystallisation systems for high speed sample preparations. The current robotic systems available allow for precise location anywhere within the reaches of the axis arms to within 10 micron precision. The user, not being limited to the predefined locations specified by more complex GUIs, has the freedom to develop processes unhindered by standard plate configurations. With the capability of line dispensing, the Synquad can match the speed of more complex multiple channel delivery systems at a lower initial cost. SynQuad systems are available for integration into more complex high throughput analysis schemes. It is this flexibility of features that make the Digilab SynQuad/Axsys systems not only a viable choice for simple liquid transfer but an integral asset in pharmaceutical research. Current innovations in liquid handling mechanics have been shown to push the limits for low volume delivery of the Synquad units into the picolitre volume range (**Figure 10**).

The **Formulatrix** (www.formulatrix.com) Tempest is a flexible reagent dispenser that is fast enough to be used as a bulk reagent dispenser, yet has a low dead volume to dispense precious reagents. The system can dispense a 1µL to a 1536-well plate in less than 14 seconds. The non-recoverable dead volume of the system is 40µL with a typical dead volume of 400µL. For precious samples, a pipette tip can be used as the ingredient reservoir to reduce the dead volume down to 100µL. A robot-accessible stage allows the Tempest to support virtually all SBS-footprint plates up to 1536-well plates in density. At the core of the Tempest is a patent-pending microfluidic chip that has 96 independently controlled nozzles. The system uses positive displacement micro-pumps to dispense any reagent into any well at any volume down to 200nL with no upper limit. The system can dispense beads and cells without any tearing/damage to the cells. The Tempest's speed comes from using the 96 nozzles to dispense multiple reagents simultaneously. The microfluidic chip supports up to 12 ingredients and can be programmed to automatically wash itself after a run of plates. The microfluidic chip is designed so the reagent moves from larger to smaller channels with the nozzles being the narrowest points. If a clog were ever to occur, the system can back-flush the microfluidic chip through larger and larger channels to remove the clog. The nozzles themselves are made of moulded silicone. They can be easily removed and replaced if a clog ever occurred there (**Figure 11**).

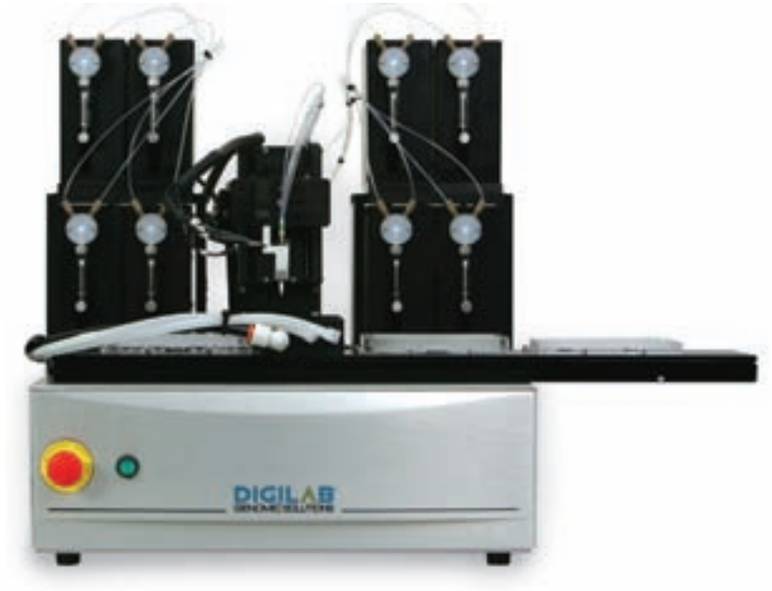

Figure 10: Digilab eight-channel SynQuad System (Pixsys configuration)

Figure 11
Formulatrix Tempest

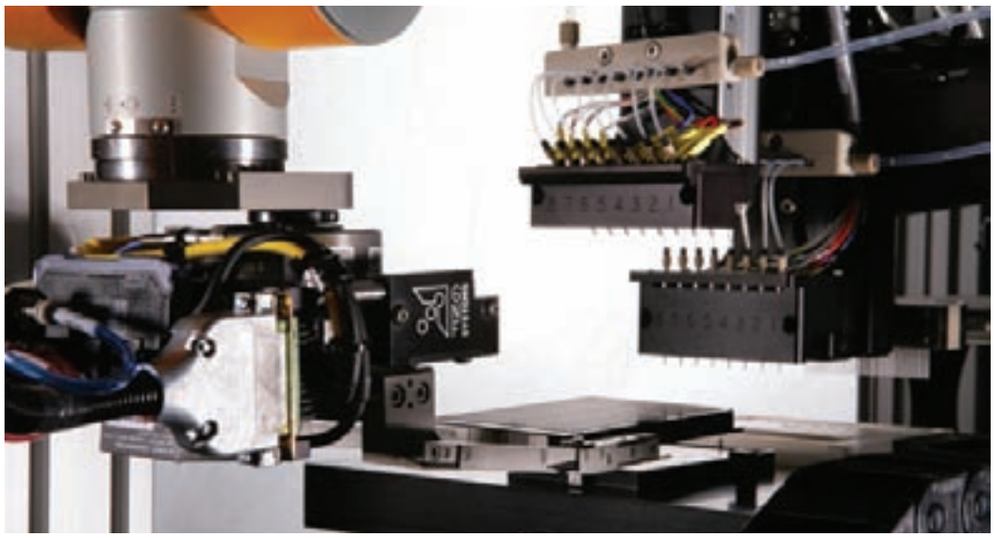

Figure 12
GNF Systems Washer/Dispenser featuring one aspiration head and two dispense heads

The **GNF Systems** (www.gnfsystems.com) Washer/Dispenser is built to industrial standards for reliable, reproducible and finely controllable aspiration and bulk dispensing applications for 96, 384 and 1536-well plate-based assays. GNF Systems developed this Washer/Dispenser to meet the needs of scientists running complex plate-based assays in miniaturised formats without compromising assay quality or speed. The GNF Systems Washer/Dispenser is available in both standalone workstation and integrated online formats. The GNF Systems Washer/Dispenser features one aspiration head and two dispense heads. The aspiration head is configurable to address single columns of 96, 384 and 1536-well plates, and this year an eight-column aspirate head was developed by GNF Systems to reduce aspiration times to less than 10 seconds for a 1536-well plate. Each dispense head contains eight tips. Each tip in a dispense head may be plumbed to a common source vessel for bulk reagent dispensing, or to an independent vessel for single tip dispensing. Great versatility is offered by functions such as any tip may dispense any volume into any well of a plate, enabling design of experiment type applications. Dispense heads contain either vertical tips for rapid dispensing, or angled tips optimised for gentle dispenses into plates with minimal perturbation of well contents (**Figure 12**).

Figure 13: IDEX Health & Science Nanodrop Express

The 16-channel **IDEX Health & Science** (www.idex-hs.com) Innovadyne Nanodrop Express system is an effective syringe/solenoid-based bulk reagent dispenser configurable with tips spaced at 4.5mm or 9mm. The system architecture (aspirate and dispense) not only benefits from an extremely low dead volume flowpath, but also facilitates the frequent exchange of reagents in assay development scenarios as well as genomic assays. Reagents may be staged in plate or reservoir formats including low dead volume labware such as 200µL conical bottom tubes. The system utilises air gaps for separation of reagents from the system fluid and minimises overfill dead volume per run. The lack of moving parts within the flow path makes it possible to use particulate laden reagents and simplifies washing and maintenance routines. Configurations utilising stirred reservoirs, specialised tip adapters and tubing constraints have been developed for dispensing bead solutions including Ytrium Oxide beads. The flexibility of the pressure system allows cells to be dispensed

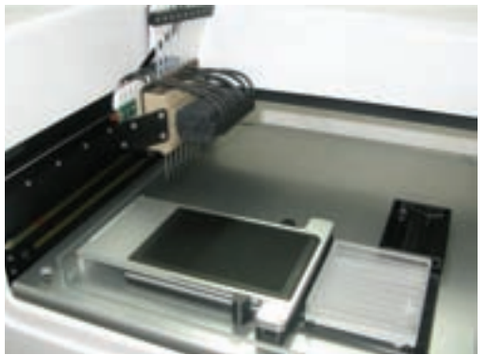

Figure 14
KBioscience Meridian WWP liquid dispenser (far left), and view of the bed with 1536 plate and eight-channel dispenser (left)

without the harmful shearing found in many reagent dispensers. Each channel of the Nanodrop Express can be individually programmed making the creation of gradients and complex plate maps possible. Worklists can be used with CSV files to accommodate normalisation assays as well as more intricate patterned dispenses. Recently developed software lets the user define the desired end result with the detailed reagent dispensing automatically generated within the software. The system is readily integrated within fully or semi-automated platforms (**Figure 13**).

The latest in the innovative instrumentation range from **KBioscience** (www.kbioscience.co.uk) is the Meridian WWP liquid dispenser. Launched in July 2010, it represents a major step forward for robust aspirate/dispense and bulk dispensing. Driven by the need for a high reliability, fast and flexible instrument for use in the KBioscience Laboratory Services Division, the Meridian has been extensively tested and is currently in use daily. The instrument has a number of features that set it apart, notably these are a solenoid/pressure valve dispensing system that is guaranteed for a minimum of four million dispenses. Each instrument is configurable from a single tip up to 16 tips per head, with each tip being individually addressable, allowing for multiple fluids to be dispensed. Coupled to this setup is an industrial motion controller that allows for fast move stop dispense motion, rather than 'on the fly' dispensing. The net result is a liquid dispenser that is ultra reliable at dispensing with speeds in excess of other available systems. The Meridian software is GUI-based and PC-controlled, enabling the dispensing of any combination of wells from any combination of tips. Programming is achieved by drag and drop selection tools, offering the user unsurpassed ease of programming dispense patterns. Released in July and in use on a 16-hour shift pattern dispensing hundreds of 1536-well plates per day, the Meridian has increased the throughput and efficiency of the SNP Genotyping Division by as much as 40% from the previously used commercial dispenser systems (**Figure 14**).

FlexDrop™ PLUS Precision Dispenser from **PerkinElmer** (www.perkinelmer.com) is the premier solution for precise dispensing of reagents, buffers, solvents and cells for today's research and screening applications, including cell-based assays, ELISA assays, Alpha Technology™, receptor binding assays, PCR sequencing setups, high throughput assay preparation and compound storage. Versatile to support a wide array of application techniques, FlexDrop PLUS easily performs non-contact dispensing into 96, 384 and 1536-well shallow and deepwell microplates. This multipurpose reagent dispenser can also accommodate dispense volume ranges of 200nL to 2mL and accurately dispenses volumes of 0.4µL into a 384-well plate in less than 10 seconds and 0.4µL into a 1536-well plate in less than 30 seconds. The integrated software allows the user to store up to 99

Figure 15: FlexDrop™ PLUS Precision Dispenser from PerkinElmer

Figure 16: Redd & Whyte Preddator S1

protocols, and gain enhanced control of all dispensing patterns, speed, volumes and chemistries. With a compact design, FlexDrop PLUS can easily fit inside a biosafety enclosure or standard laboratory hood to provide a sterile environment and ensure the safety of the technicians while dispensing liquids, media or other chemistries. In addition, it can easily be integrated to liquid handling workstations such as PerkinElmer's JANUS® Automated Workstation to enhance automated sample preparation techniques, and reduce manual intervention. High throughput microplate processing, dynamic volume range, exceptional accuracy and precision, and the ability to dispense up to four reagents across a single microplate delivers a dispensing solution for today's researchers looking for optimised methods, improved results and more quality data (**Figure 15**).

Redd & Whyte (www.reddandwhyte.com), a specialist provider of novel liquid handling technology, has just launched the Preddator S1, a unique instrument designed for dispensing low volumes of cells, beads, and biochemical reagents into 96 to 3,456-well plates. Redd & Whyte sees a growing requirement to dispense increasingly complex reagents in drug discovery and life science research applications at sub-µL volumes. However, current dispensing technologies are inadequate at high throughput, often causing problems such as blockage of tips; damage to cell samples; foaming of surfactants and detergents; and are largely ineffective dispensing of oils. The Preddator was designed specifically to overcome these problems across a wide volume range (20nL to 100µL), and developed after extensive consultation with leading scientists in the pharmaceutical industry. It ensures highly accurate and repeatable dispensing of biological materials into all types of microplates, including those with peripheral evaporation wells and channels. It can be programmed to dispense any pattern – even curves. The Preddator's dispense technology is based on a solenoid valve, designed to function with high reliability and minimal clogging. Its simplified fluidic pathways allow cells to pass through the valve unharmed; accuracy is typically 2%CV across a 1,536-well plate when dispensing cells at 500nL, with more than 95% viability. The user can select the dispensing pressure and volume, providing ultimate flexibility for effective dispensing of detergents and highly viscous oils. The Preddator can be used as a standalone instrument or integrated within an automated robotic platform. It is modular in design and can be upgraded to a four- or eight-channel system, with options for auto calibration, tip cleaning, plate stackers and cooling racks (**Figure 16**).

Thermo Scientific Multidrop (www.thermoscientific.com) dispensers, based on peristaltic pump technology and disposable dispensing cassettes, are widely used for dispensing different reagents, buffers and cells into various microplate formats. The latest development in the product group, the Multidrop Combi, enables routine use of the 1536-well plate format by allowing reliable dispensing of small volumes down to 0.5µL with excellent precision. The instrument can be integrated into any automated system, which allows for full walk-away automation of most assays, which combined with miniaturised assay volumes result in cost savings through minimised reagent consumption and increased throughput. The technology behind the instrument and the use of a disposable dispensing cassette make the unit optimal for dispensing live cells with reproducible results without the fear of cross contamination. The option to use plate types ranging from 6-well up to 1536-well plate format accommodates different users performing a wide

Figure 17: Thermo Scientific Multidrop Combi nL low volume dispenser

diversity of cell-based assay types and applications. One of the Multidrop instruments, the Multidrop Combi nL, utilises a different type of dispensing technology based on solenoid valves and a pressurised reagent vessel, which allows for dispensing volumes at the nL level and makes the instrument a powerful tool in a growing number of assays requiring the use of a minimal amount of reagent, including the assay development phase as well as primary screening. In addition, when used with Thermo's intuitive FILLit Software even more features and flexibility can be achieved with Multidrop instruments. One of the most powerful features of all the Multidrop instruments is their overall simplicity, which allows any user to come up and fill their plates without a need to go through an extensive training session or user manual to ensure the success of the work (**Figure 17**).

Kalypsys Systems (now part of Wako USA's automation division) (www.wakousa.com/automation) has added a powerful new option to its well-established 1536/384 Bulk Dispenser/Plate Washer. Tip clogging is the number one issue with all bulk dispensers on the market today. Kalypsys has addressed this challenge by offering a clog detection and automated recovery module. Clog detection provides immediate feedback on the dispenser's performance. The software allows a user to define the parameters used to determine if a clog has occurred. Once a clog is detected, a user can be alerted and/or the automated clog recovery routine can be activated. The automated recovery routine will automatically disable the clogged tip, and utilise a different tip to dispense to the wells assigned to the clogged tip. The bulk dispenser comes with two dispense heads each with eight tips. If an unusually sticky or clumpy reagent is dispensed, the detection and recovery software will allow the dispenser to continue to operate even after seven of the tips on one head become clogged. Wako's 1536/384 Dispenser/Plate Washer developed by Kalypsys is the only bulk dispenser washer on the market that can detect and automatically recover

Figure 18: 384/1536 DA unit with clog detection and recovery from Wako Automation, powered by Kalypsys Systems

Table 1: Comparison of bulk reagent dispenser offerings

VENDOR	INSTRUMENT NAME	DISPENSE MECHANISM	WORKING VOLUME RANGE	SPECIAL FEATURES
Beckman Coulter	BioRAPTR FRD Microfluidic Workstation	Micro-solenoid valve	100nL to 60mL	Dispense up to 8 reagents in one pass with flexibility of independent volume control and well selection
BioTek	MultiFlo™ Microplate Dispenser	Unique combination of peristaltic pump and syringe drive technologies	1µL to 3mL	1-to-4 reagents, 6- to 1536-well plates, fully modular and user upgradable
Digilab	Presys, Pixsys, Microsys	Synquad solenoid valve/syringe pump	20nL to >5µL	User control of movement and dispensing functions
Formulatrix	Tempest	Positive displacement micro-pumps	200nL with no upper limit	Independent channel control, can unclog itself, two separate wash inputs, removable nozzles, can dispense beads/cells
GNF Systems	GNF Systems Washer/Dispenser	Pressurised reagent source vessel with solenoid valve metered dispense	200nL to 1mL in 10nL increments	Optimised for aspiration and dispensing in complex, and cellular, assays in 96/384/1536-well plates
IDEX Health & Science	Nanodrop Express	Solenoid valve/syringe	50nL to 500µL	Valve free flow path
KBioscience	Meridian WWP	Solenoid/pressure valve	0.3µL to mLs	Individually addressable tips – capable of user determined pattern dispenses
PerkinElmer	FlexDrop PLUS	Solenoid valve	200nL to 2mL	≤ 5% CV for volumes as low as 500nL and integrated stackers for unattended reagent dispensing
Redd & Whyte	Preddator S1	Solenoid valve	20nL to 100µl	All reagents including surfactants, cells, beads, biochemicals & oils. All MTPs up to & including 3456
Thermo Fisher Scientific	Multidrop Combi	Peristaltic pump	0.5µL to 2.5mL	6-1536 plates, automatic plate height adjustment, SMART option for consumable lifetime traceability, automation friendly, FILLit Software
Thermo Fisher Scientific	Multidrop Combi nL	Solenoid type of valves	50nL to 50µL	96-1536 well plates, individual channel control, ready made calibrations for quick start, automation friendly, FILLit software
Wako Automation (formerly Kalypsys Systems)	384/1536 DA with Clog Detection and Recovery	Solenoid valve	0.2µL to 500µL	1536-well plate washer; automated clog detection recovery, one straight and one angled dispense head

Reference

1 Bulk Reagent Dispenser Trends 2010 Report, published by HTStec Limited, Cambridge, UK, March 2010.

from clogged dispense tips. It enables the production of high quality data and uninterrupted runs, even under the harshest conditions (**Figure 18**).

Discussion

Table 1 compares the main BRD offerings and highlights some of the information detailed in the vendor snapshots. What is evident from this table is that most of today's BRD systems utilise some sort of solenoid valve, many are pressurised. The exceptions are BioTek's MultiFlo™ Microplate Dispenser and Thermo Scientific's Multidrop Combi, that rely mainly on peristaltic pump technology and Formulatrix Tempest that uses positive displacement micro-pumps. Although the actual working volume dispense range varies between instruments, all systems reported cover the range 1µL to 5µL, and most have a significantly lower dispense capability. The extent to which a very low end (ie below 200nL) capability is really needed for the predominant BRD applications (see **Figure 1**) is debatable. Nearly all BRD systems today are able to address the 96, 384 and 1536-well plates, however some with larger dispense volume capabilities also address 6-well plates. Many of the BRD systems reviewed have the flexibility to dispense multiple reagents, in some cases this is achieved in the same pass with multiple dispense heads, in other instruments individual channels are addressable and controlled separately enabling any tip to dispense any volume into any well of a plate. This versatility is utilised by some vendors to provide a design of experiments capability within their software. Simplicity in instrument operation and/or software are critical for those users who just want to walk up and dispense, however, most vendors also support greater dispensing flexibility through intuitive GUIs and powerful control software permitting user determined patterned or even gradient dispensing. HTStec's survey showed that tip clogging was the most problematic aspect of BRD dispensing today, so the ability to replace clogged tips or remove the clog is essential. The availability of systems able to automatically detect clogged tips and then to initiate a clog recovery routine mid-run represents a big advance, particularly for some integrated system users. A few BRD systems have angled dispensing for delicate adherent cell applications and some of these are combined with a plate washing (aspiration) capability that now extends to 1536 plates. Overall today's BRD are very much improved in terms of their capabilities, performance and software control over those obtainable 10 years ago. Many features which users could only dream about are now available as standard. However, improved BRD reliability and robustness still seems to be an elusive goal, it remains the biggest cause for concern particularly among high throughput users and a major influence on future purchasing decisions. Time will tell if the generation of BRDs discussed in this article will adequately address these concerns and if true industrial standard reliability has now been achieved. One thing for sure is that BRDs are likely to be a common sight in all labs requiring fast plate filling for the foreseeable future. DDW

Dr John Comley *is Managing Director of HTStec Limited, an independent market research consultancy whose focus is on assisting clients delivering novel enabling platform technologies (liquid handling, laboratory automation, detection instrumentation and assay reagent technologies) to drug discovery and the life sciences. Since its formation seven years ago, HTStec has published more than 50 market reports on enabling technologies and Dr Comley has authored more than 30 review articles in* **Drug Discovery World**. *Please contact info@htstec.com for more information about HTStec reports.*