Advances of laboratory automation for drug discovery

Laboratory automation has metamorphosed the realm of drug discovery over the years through two of major influential factors – cost benefit and error reduction. Automation has reframed the traditional drug discovery process by making feasible the identification of many targets through the biotechnology revolution and various combinatorial technologies that have fuelled compound collection. Automation of compound management processes has minimised late stage compound drug rejections which are also backed up by pioneering efforts taken in the field of high throughput screening. The automation market brings a diverse array of tools for the bio-pharma community and given the immense expenditure on R&D, enables the lifting of bottlenecks in many processes downstream to target identification and screening.

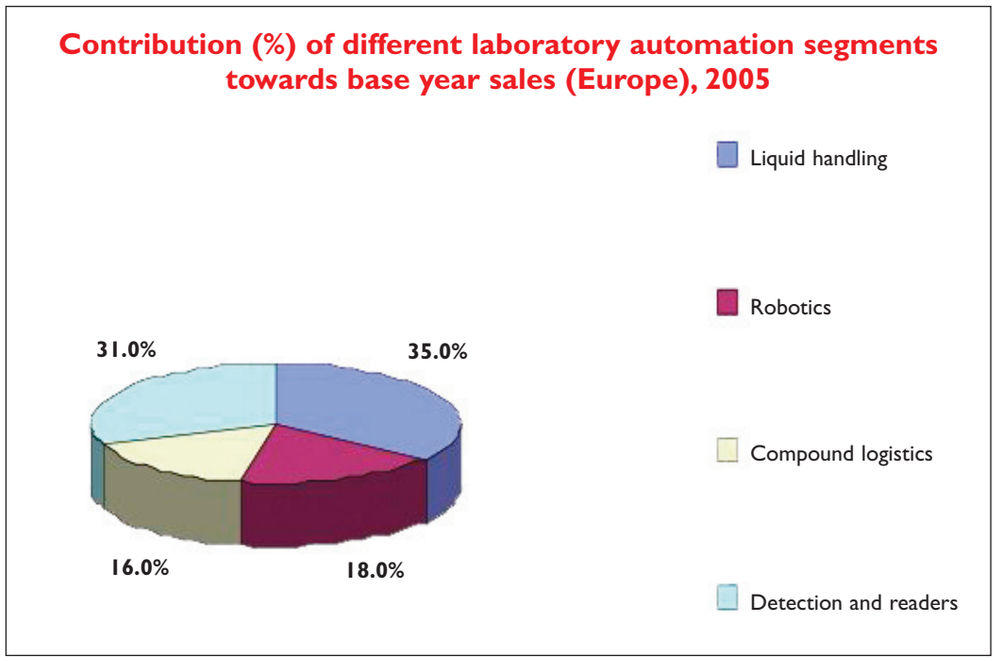
By Charanya Ramachandran

The overall lab automation market within western Europe alone has been estimated to be around $245 million in 2005. With economic vagaries encumbering many lifescience companies in Europe, automation of many experimental procedures seems to be a crucial step as streamlining of workflow can be achieved with lesser error and better precision. Automation is most needed where there are tasks of repeatability and would thus reap better financial returns while saving on the skilled labour force. The current trend of opting for mechanisation has been ascending and drug discovery laboratories would like to optimise by identifying compounds at an early stage and thus save huge time and costs.

Robotics has carved a niche in the field of drug research. Having undergone many cycles of innovation, robotics has given the boon of flexibility that has lured researchers to incorporate industrial robots in their routine processes. Many applications include pick and placing sample vials, cherry picking compounds thus enhancing the speed of assay preparation. The robotics market for drug discovery applications contributes to a little less than 19% of the overall lab automation market with a compounded annual growth rate (2005-2012) of around 8%.

The market lifecycle for the overall laboratory automation market is in the late growth phase. **Figure 1** illustrates the major segments that make up the entire automation for drug discovery purposes. With the liquid handling and detection market segments making the most contribution to the average base year sales with 35% and 31%

Figure 1
The impact of market drivers on the laboratory automation market over the period 2005-2010



share respectively. While liquid handling and robotics have witnessed many technology improvements over the past decade, the segment is placed at the late growth phase where there is still volume for expansion owing to them being ubiquitously used in modern drug discovery. On the other hand, the detection segment seems to have captured the spotlight with many opportunities for growth. **Figure 2** depicts the market lifecycle for the different automation product segments discussed.

Other automated product segments include compound handling and inventories with a moderate growth owing to pharmaceutical companies requiring better quality in the samples. Automated incubators is another niche area seeing a lot of brighter prospects especially with the thrust from the implementation of cell-based assays.

With the revolutionary approach in drug discovery, automation and information technology are the two supporting arms that bolster the entire modernised drug discovery paradigm.

Lab Automation on a generic level, is classified into:

- Unit or modular automation
- Total integrated system platform

The individual segments that are encompassed in the aforementioned classes are:

- Liquid handling workstations
- Robotic systems
- Other automated product markets
  - ❍ Compound handling
  - ❍ Microplate readers

Application of automation in drug discovery

- Therapeutic areas (target identification and validation)
- Screening
- ADME toxicity studies

Miniaturisation and cell-based assays take the front gear in today's drug discovery

With laboratory automation technology undergoing further innovation, the trend is heading towards miniaturisation with the hope to gain a phenomenal saving on consumables. High throughput screening mechanisms have undergone radical changes in the past few years with many disruptive technologies yielding better results and necessitating a parallel improvement on the supporting instrumentation. Reducing the volume and increasing the capacity by a factor of four has shrunk the well size resulting in a high density format. The proclivity towards flexible automation systems and the requirement for scalable solutions are also witnessed in the European lab automation market.

Standardisation of assays is another notable trend perceived in the European drug discovery segment

with high content screening (HCS) analysis taking the centre stage in the screening process. Initiative on consolidating protocols between suppliers and research laboratories has enabled faster transfer of assays to screening. Progressing from 96 plate format to 1536 high density format pharmaceutical companies are expecting to maintain the throughput and remain competitive. Presently 384 plate format has ushered in confidence amidst the pharmaceutical research community in terms of cost savings and efficiency apart from the bolstered support from corresponding detection and dispensing instruments. Suppliers estimate that the 96 well plate format may phase out in the near future with a continuing use of 384 plate format and a consideration as to the pending challenges addressed with 1536 well plates. Higher numbers of wells and smaller liquid dispensing capacity along with robotic systems can help maintain the throughput for HTS.

Cell based assays are representing close to 40% of the screening methods and in therapeutic areas. This new approach has shown a ray of hope that there will be some economical gains with the lead generation process and thereby has a reasonable success rate with newly found therapeutic targets. The demand for highly sensitive reading technologies is perceived especially with the lift force from HCS. Although higher densities and low volumes have been achieved, there have been many teething troubles with balancing the instrument capabilities and the rising reagent costs.

The completion of the human genome project heralded the start of a high throughput screening process that made feasible screening of close to 100,000 assays per day. Automation has truly given a good edge for screening capabilities than the traditional process. With the knowledge of genome sequences, low cost robotic liquid handlers are now being aimed at medium and low throughput systems especially with the huge information churned from the high throughput screening process. The concept of total lab automation is currently afforded by some big research laboratories and the top 20 pharmaceuticals.

Automated compound handling markets key to stepping up drug discovery

Screening capabilities have compelled the need for augmenting a smarter drug library to maximise the efficiency of HTS. The very basis for any screening technique are compound libraries. The physiochemical properties of the compound are critical in determining the shelf life. With an accelerated drug discovery process, compound management has become the cornerstone to enable successful primary and counter screens for selecting candidate leads and ensuring selectivity.

Compound management has lent itself to automation by gradually adapting to robotic and automated dispensing environments for plate reformatting accordingly, keeping in pace with

Figure 2

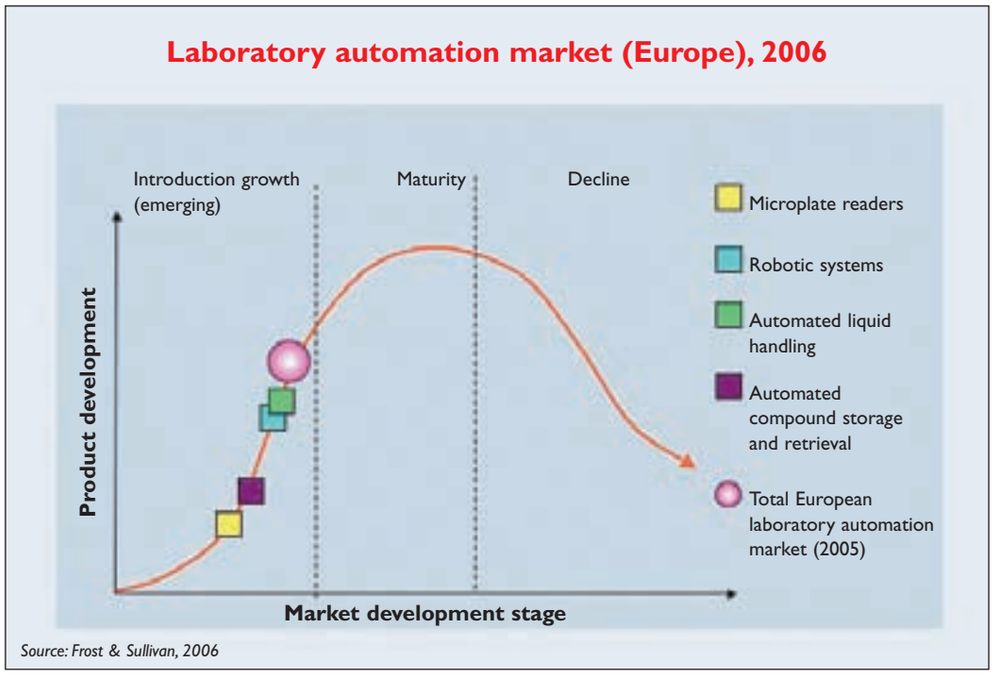
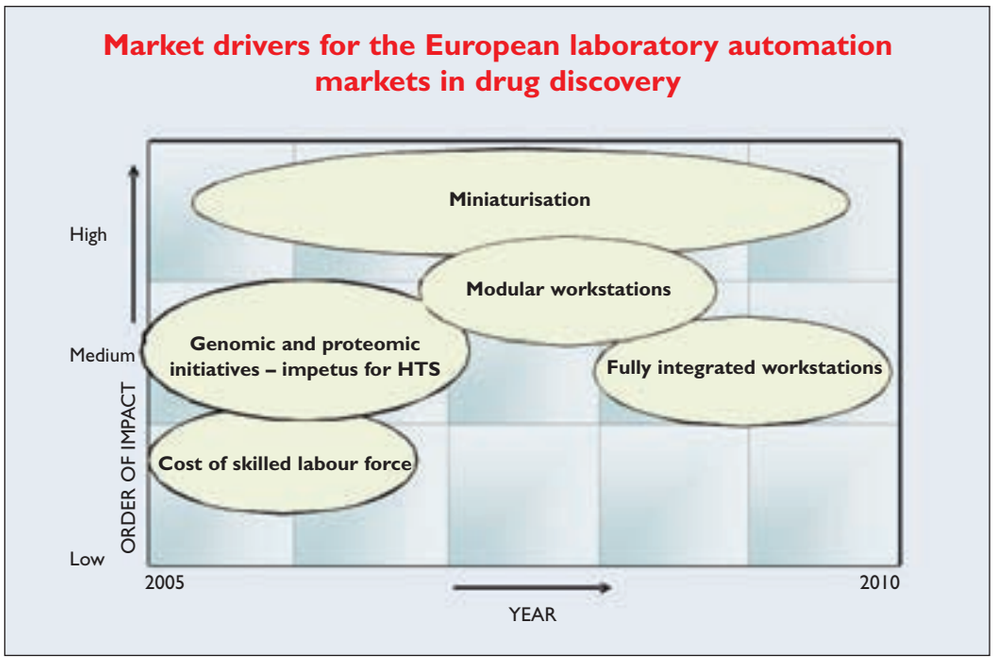


Figure 3



the miniaturised plate formats. Automated compound handling has matured in a comparable manner to the other segments in microplate instrumentation. Ensuring compound accessibility and maintaining its integrity are some of the salient underlying parameters while designing an automated compound inventory. There are semi-automatic and fully automated sample storage and retrieval systems controlled by software and robotic arms respectively.

Sample tracking is yet another important segment in sample management which holds a repository of sample information elucidating the characteristics, identification and results. It is very critical that every sample accessed is thoroughly verified before dispatch at the right concentration and volume. Although this is an error-prone sector owing to huge compound handling, an amalgamation of an efficient logistics design bolstered by smarter informatics solutions can help reduce false positives and further the prospects of automated compound management in the future.

This sector is witnessing a fast-paced growth with the emphasis of fulfilling the ever-changing research needs especially with the spiralling compound sets every year.

Integrated workstations: drug laboratories nurture the growing trend

The current trend is best described as the polarisation towards looking at modular integration units rather than purchasing robotics or individual mechanised components. Bigger laboratories typically prefer a holistic workstation platform whereas the smaller and the mid-sized laboratories may opt for flexible and cost beneficial units that can be incorporated into a larger platform in the future. Thus, the configurability of modular units is the keystone to the development of automation owing to changing experimental needs in biological assays. Robotic arms facilitate the required flexibility for carrying out processes like sample vial transfer, liquid handling operations and serve as a salient feature in the robotic workstations.

While the modular concept is receiving heightened appreciation, there may be some restraints deterring the acceptance of a total large scale laboratory system. On the one hand, premium costs may withhold the uptake of this idea. Secondly, establishing communication between the various devices and ensuring proper sample tracking and data management with the corresponding LIMS system can be a challenge. Owing to the complexity of biological assays and the overall integrated model it may be difficult to reconfigure to varying assay formats and there will be a trade-off with flexibility. Overall functional operation with minimal downtime of instruments is also another point to ponder from the end-user perspective.

Flexibility versus speed: is the trade off reasonable?

The drug discovery industry certainly is heading towards seeking more fruitful rewards from the automation markets. Automated liquid handling workstations backed up by robotic systems have provided an added dimension of flexibility. These systems have reinstated the benefit of having a specialised modular work cell for custom-made tasks. These work cells should be built on an open platform technology such that there is compatibility with other equipment further integrated on and thus illustrating the key of configurability. The aforesaid approach can possibly bring in good ROI for drug research companies.

Liquid handling technology has been one of the foremost segments in automation over the past decade from simple pipetting to ultra-high precision dispensing methods. Industrial robotic systems have also contributed to the development of automated liquid handlers and other workstations. Automation is the key where enormous samples have to be tested in a given timeframe. With the continual trend of HTS-based drug discovery, liquid handling systems have been coping to handle a variety of volumes from millilitres to the nanolitres range. Sample transfer between different stages is another prevalent issue and logistics ought to be worked carefully to maintain the number of screening tests for consistency. Flexibility or robustness is one of the key questions faced by every laboratory. Although a tough choice to juxtapose, it is essential that every laboratory understands their requirement level for automation as there is no one size befitting every laboratory.

The advent of microfluidics has opened up the horizons to further the scope of HTS methodologies. Working on the concept of laminar flow, it is hoped that a microfluidic approach will ease out pain points with respect to reagent dispensing and thus making assay miniaturisation and compound inventories a more pragmatic reality. With Caliper Lifesciences having provided the flavour for this technology, it has been well embraced amidst the HTS screening laboratories as there is a combination of fluidics technology with detector readouts

on the same platform. Although atom size volume handling is grappling with the challenges of balancing out costs of reagents, this technology is still in the early adapter phase. Compact disk micro-laboratories are being fostered for basic research as they bring in two advantages of miniaturisation and integration thus helping improve laboratory productivity by parallel sample processing. However, whether these embryonic technologies will cope up to the required throughput is still to be estimated.

Data handling poses some teething troubles

Automated assay development and the shift towards high content screening have churned mixed reactions. Modern detection technologies are required to facilitate multi parameter readouts thus throwing pressure on the data handling procedures and thus demanding more sophistication. With the surge of biological data, there is a big challenge for smaller companies to sustain the increasing competition as they would have to bring in upgrades of user friendly and cost beneficial software to keep abreast with the flux of the market.

Automation, having concomitantly brought in productivity changes, has left a stumbling block in the data interpretation module. Simple issues such as manual microplate labelling can appear detrimental to data transcription even if one plate gets invalidated. Furthermore, in order to avoid any incompatibility issues with software and microplate instrumentation, it is essential that the relevant data archival is conducted throughout the experimentation time. Drug research firms require complete solutions with dedicated customer care thereby realising their value for the huge investments. Research laboratories also expect maximum flexibility with the software such that they can configure it themselves.

The European laboratory automation market for drug discovery applications is highly fragmented with a diluted market concentration. The automation market comprises 30-40 suppliers for lifesciences automation that can be represented by a combination of some globally represented participants and players at national and regional levels. Brand recognition is one of the foremost barriers to entry along with the ability to bring forth cost-effective integrated solutions. The innovators in the microfluidics and nano volume handling can impact the market dynamics as miniaturisation is expected to be a positive driving factor for the next few years. These companies can hope to improve their market share by addressing the current challenges and providing user-friendly products.

Owing to the requirement of complete solutions as opposed to stand alone technical tools, there has been realignment in the competitive framework with many companies looking for mergers and acquisition (M&A) opportunities such that they can improve their competitive strategy by expanding their product portfolio through vertical integration of different technologies on the same platform. The M&A trend coupled with technology licensing is likely to continue in the next few years yielding a fairly rationalised automation market with a strong focus on integration. Secondly, this development will provide researchers with assays, consumables, detection and liquid handling facilitating more scalability through simplified robotics for ease of use and provide the differentiating factor for manufacturers to keep up the competitive leading edge.

Experience and adeptness describe the laboratory automation market in a snapshot. Research findings encourage synergy between automation solution providers and drug research laboratories for effective rendering of technology applications in a palatable manner thereby assisting scientists to focus well on effective data analysis. Furthermore, in order to address the downstream data handling bottleneck, it is best advised for automation suppliers to partner with complimentary LIMS business solution providers. This gives a major lucrative benefit of gaining visibility and winning customers' support as a full fledged solution and a service provider. Modularity concept with miniaturisation would continue to drive productivity in the drug research labs with longer walkaway times. With a transition towards cell-based screening, efforts have been targeted to configure a cohesive work cell that would establish effective communication between the multiple workstations and other equipment in a cost-effective manner. DDW

Charanya Ramachandran *joined Frost & Sullivan in the capacity of a Research Analyst in February 2005. Her key focus area has been drug discovery technologies for the European healthcare practice. Her role involves identifying, researching and analysing key market drivers, challenges and potential of the European Drug discovery industry. In addition to this, Charanya had made editorial contributions viewed on Frost's web portal as well as a few European journals. Prior to joining Frost & Sullivan, Charanya was working with the Department of Biomedical Engineering at Texas A&M University, USA as a Research Assistant in the Tissue Engineering Laboratory.*

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