

High-throughput screening robot

# Automating R&D

Technology addresses the need for increased productivity and efficiency.

BY KIMBERLY S. CLEAVES

Since the introduction of laboratory robotics, the concept has evolved from a curiosity to a phenomenon; modern drug discovery is now predicated on automated instrumentation, experimentation, and analysis. For example, the onset of the race to map the human genome helped drive the need for robotic and automated methods in gene sequencing and data handling. From finding targets to designing drugs that will bind them to assaying the results, R&D in pharmaceuticals, genomics, proteomics, and molecular diagnostics relies on automated technologies.

Since the development of Unimation's industrial robot in the early 1960s, subsequent improvements in computer control and a reduction in size have given rise to devices that are practical for clinical laboratory operations. And the history of laboratory automation parallels the progression of drug discovery approaches within the pharmaceutical industry. Automation now encompasses a wide variety of functions and processes used in the broader life sciences industry.

The first robot specifically geared toward lab automation was

the Zymate, created in 1981 by Zymark's co-founder, Burleigh Hutchins. This robot was easily adapted and successfully applied to preanalytical sample preparation and to potency and stability testing in the drug industry.

By 1983, "productivity" was the buzzword at the Analytical Laboratory Managers Association Conference at Purdue University and was often used as a rationale for robotic automation and systems. This sparked fierce competition as first Perkin-Elmer and next Fisher Scientific introduced their robotic models. The Zymate robot was dubbed the "one-armed chemist" by *Forbes* magazine and was on its way to starting a new era in laboratory operations.

In the past 20 years, the industry has seen a dramatic expansion in the number of automation manufacturers. Zymark itself was acquired by Caliper Technologies, now Caliper Life Sciences ([www.caliperLS.com](http://www.caliperLS.com)), in mid-2003. And the number of cooperative agreements between vendors and life sciences companies, where the goal is to speed up the rate of drug discovery, has increased as well.

## Robotics for science

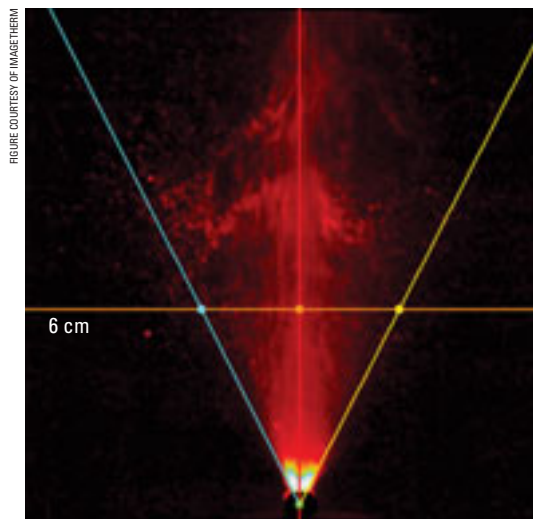
The Allegro system is a good example of a "shared investment" born out of a cooperative collaboration between companies such as Zymark, Johnson & Johnson (J&J; [www.jnj.com](http://www.jnj.com)), and

Boehringer Ingelheim GmbH ([www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)). Designed to eliminate bottlenecks, the Allegro system automates high- and ultrahigh-throughput screening applications and high-speed plate preparation. It is a scalable robot that interconnects 25 or 26 different modules. The basic workstation module contains at least one robotic arm, is mobile, and can be re-configured for a variety of assays. It is designed so that each module performs a single step in an assay, and every step takes a minute or less to complete.

At J&J, a screening team of researchers first develops either in vitro or cell-based assays, depending on the nature of the drug targets. And after outlining and setting up the assays, the team validates them by using either robotic or manual technologies, or a combination. After the Allegro robotic assay is developed, the compounds undergo primary, secondary, and possible tertiary screenings. Following consultation with the company's therapeutics team to select potential hits for follow-up analysis, the screening group proceeds to further validate selected lead targets.

Similarly, Carol Homon, associate director, biomedical screening, department of inflammatory diseases at Boehringer Ingelheim, was looking to automate screening procedures. "We can reconfigure for different screening methods as needed, which lets us perform HTS assays in the optimal manner for each assay type," she says.

The modularization of robotic laboratory products is one of many rapidly evolving trends. Other visible trends in automated



**Spray pattern image** of plume geometry measurements from a nasal-spray pump, collected by an automated testing system, shows plume angle and plume width of the vertical orientation of the laser light sheet relative to the pump nozzle.

applications are fewer stand-alone robot arms, in part because robotics is being directly integrated into laboratory devices, and the development of automated devices to replace manual tests for applications such as spray drug technology.

The Allegro system was developed out of a "drive to miniaturization," says Kevin Hrusovsky, president and CEO of Caliper Life Sciences. It also is a product of a new approach to product development using interdisciplinary technologies and cooperative efforts. It's an example, he adds, of an area in which companies such as J&J "have done a lot of underwriting of major products that are now serving industry."

Another example of the "shared investment" model Caliper employs is

its Drug Discovery Consortium, between Caliper and companies within the industry, to develop upgrades to its standard assay workstations. Hrusovsky points out, "The products that are being developed in the context of this consortium demonstrate the applicability of Caliper's technologies across the entire drug discovery pipeline, and highlight our ultimate goal of delivering a broad spectrum of tools that will help our customers bring drugs to market."

## A growing market

In the drug industry, where productivity is paramount and the stakes are high, new automation tools will inevitably be required. According to an assessment by Front Line Strategic Consulting ([www.frontlinesmc.com](http://www.frontlinesmc.com)), "The proteomics market is expected to grow rapidly throughout the next 5 years, reaching a value of nearly \$3 billion by 2005." However, for the market to reach those levels, it would

## Automated facilities

"The pharmaceutical-biotechnology industry can historically be considered a late adopter of manufacturing-focused automation technologies," says Clive Smith, industry marketing manager at Andover Controls ([www.andovercontrols.com](http://www.andovercontrols.com)), referring to regulatory compliance involved in automation in manufacturing.

"But from a facility-automation standpoint, the situation is quite different. Pharmaceutical-biotechnology company facilities often employ some of the most advanced building automation technology available," Smith adds, for monitoring buildings.

Ever more important is the critical role automated systems play in facilities monitoring as well as in attaining and maintaining regulatory compliance in life sciences applications. With a recent near-exponential increase in the number of FDA Warning Letters, many of which include citations of noncompliance with 21 CFR 11, the scope and the importance of this new regulation are quickly

becoming apparent. However, interpretation of and adherence to this complex regulation, which covers electronic record-keeping, are under evaluation and may possibly be reissued in coming years. Part of the debate is, when does a record become an electronic record and subject to the regulation?

Andover manufactures facility automation systems for the biotechnology and pharmaceutical industries, and, through its Continuum Facility Management System, provides HVAC control, badging, security alarm monitoring, video surveillance, access control, and environmental monitoring for regulated facilities. As with all automation techniques, individual companies develop their own solutions based on widely varying criteria. By using automated systems to move toward fully paperless environments, companies can automatically or on demand produce electronic reports containing 21 CFR 11 records of all critically related events and parameters.

### Some companies involved in robotics and automation

Advanced ChemTech	<a href="http://www.advancedchemtech.com">www.advancedchemtech.com</a>
Amersham Biosciences	<a href="http://www.amersham.co.uk">www.amersham.co.uk</a>
Andover Controls	<a href="http://www.andovercontrols.com">www.andovercontrols.com</a>
Applied Biosystems	<a href="http://www.appliedbiosystems.com">www.appliedbiosystems.com</a>
Beckman Coulter	<a href="http://www.beckmancoulter.com">www.beckmancoulter.com</a>
Bio-Rad	<a href="http://www.bio-rad.com">www.bio-rad.com</a>
Bohdan Automation	<a href="http://www.bohdan.com">www.bohdan.com</a>
Bruker Daltonics	<a href="http://www.daltonics.bruker.com">www.daltonics.bruker.com</a>
Caliper Life Sciences	<a href="http://www.caliperLS.com">www.caliperLS.com</a>
CRS Robotics Corp.	<a href="http://www.crsrobotics.com">www.crsrobotics.com</a>
Genomic Solutions	<a href="http://www.genomicsolutions.com">www.genomicsolutions.com</a>
Gilson, Inc.	<a href="http://www.gilson.com">www.gilson.com</a>
Hamilton Co.	<a href="http://www.hamiltoncompany.com">www.hamiltoncompany.com</a>
ImageTherm	<a href="http://www.imagetherm.com">www.imagetherm.com</a>
J-KEM Scientific	<a href="http://www.jkem.com">www.jkem.com</a>
Micromass	<a href="http://www.micromass.co.uk">www.micromass.co.uk</a>
Protein Technologies	<a href="http://www.pti-instruments.com">www.pti-instruments.com</a>

For a more extensive list, visit LabGuide at [www.labguideonline.com](http://www.labguideonline.com).

likely have to be boosted by the continuous development of automated devices to keep up with the demands of drug development.

For example, at Argonne National Laboratory ([www.anl.gov](http://www.anl.gov)), a robot on loan from Beckman Coulter ([www.beckmancoulter.com](http://www.beckmancoulter.com)) is being used to construct modified bacteria to produce new proteins for advanced structure determination. The researchers are translating existing experimental protocols into software to operate the robot, optimizing their procedures to match its capabilities. The goal is to develop biochemical characterization methods for most proteins and then to automate the analysis to produce 500 new protein structures per year.

“We have seen significant efforts made to automate laboratory testing using robotics and other related technologies, and to automate systems in pharmaceutical spray-drug development, testing, and manufacturing applications,” says Dino Farina, CEO and president of ImageTherm ([www.imagetherm.com](http://www.imagetherm.com)). “The primary goal is reducing user bias and subjectivity while improving throughput and operational efficiency.”

ImageTherm’s technologies are geared toward improving pharmaceutical spray-drug product testing and efficiency by automating data acquisition, processing, and analysis. “This approach has allowed us and our users to focus on breakthrough technologies

instead of manual procedures,” Farina adds.

Both innovator and generic pharmaceutical companies, such as IVAX Laboratories ([www.ivax.com](http://www.ivax.com)) and Muro Pharmaceutical ([www.muropharm.com](http://www.muropharm.com)), are developing spray-drug products, including nasal sprays and metered-dose inhalers, using ImageTherm’s SprayVIEW technology. That system can perform a variety of in vitro studies to meet regulatory recommendations and requirements, as well as perform automated spray-pattern and plume-geometry studies for spray-drug products. “The automated actuation system uniquely adheres to the Food and Drug Administration’s latest guidance recommendations for their ability to simulate human hand actuation,” Farina says. The FDA also uses the company’s system for research and data verification.

From spray-drug development to proteomics to the programs that integrate, monitor, and maintain automated instruments, the drug industry is well versed to benefit from applications that take data, manage it, and actually use it for analysis. However, the potential of robotics and automated systems in pharmaceutical applications and the benefits for medical research are still great. Whereas Caliper’s acquisition of Zymark integrated the low-volume liquid-handling capability of Zymark’s laboratory robots with Caliper’s microfluidic expertise, advances in HTS screening and the blossoming protein applications market are attracting even more companies with innovative technology to the automation sector. ■