

MICROFLUIDICS ENABLES FASTER INNOVATION CYCLES

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A revolution has occurred in the ability of microfluidics to address challenges in the drug discovery industry. This revolution, catalyzed by the combination of microfluidics and automated liquid handling, has transformed a “whiz bang” technology into a reliable, standardized platform for generating reproducible, high quality data. Already, pharmaceutical companies such as Aventis, Pfizer, Amgen, Serono, and Eli Lilly are leveraging the power of microfluidics to develop new approaches to drug discovery. Suppliers of drug discovery technology – companies like Affymetrix, Agilent, Bio-Rad, and QIAGEN – are also harnessing this power to enhance and develop innovative products for the industry.

Microfluidics has the connotation of being a tool, when in fact; it is an enterprise discovery technology platform that can strategically transform the approach to discovering drugs. This platform can change a company’s overall information management to enable a more efficient experimentation process, ultimately leading to faster innovation cycles.² Microfluidics systems are much more than just a chip – they are actually data engines that are electronic, have high precision, high accuracy, and are very versatile. These engines are easily deployed across all of the system biology nodes and can enable organizational learning that is not otherwise available.

Five years ago, the landscape of microfluidics was messy and the technology was immature. The intellectual property was carefully guarded and problems existed with clogging and reliability. Microfluidics has always had appeal, but scientists worried about the platform’s real world applicability.

“It’s nice that it’s miniaturized, but how does it scale? I need to be able to address it as well. It’s one thing to have something that will sit on a postage stamp and can analyze 10,000 samples, but if I have to load each well with a capillary and can only deliver 500 per day, it isn’t helpful.”

Marc, Navre, Sr. Director of Leads Discovery, Syrrx, Inc.

Today, the technical challenges have been overcome. By eliminating variations in sample preparation, reaction conditions, and detection methods, microfluidics provides consistently high quality data. The versatility of the technology is allowing its application to areas such as genomics, proteomics, high throughput screening, and even molecular diagnostics.

¹ Caliper Life Sciences and Frost & Sullivan (Cosper).

² For a discourse on the relationship between experimentation cycles and innovation, see Thomke, Stefan Experimentation Matters: Unlocking the Potential of New Technologies for Innovation. Boston: Harvard Business School Publishing, 2003.

The Evolution of Caliper Life Sciences

Caliper has listened to the perceptions and concerns of scientists and has taken action. Recognizing that developing “lab-on-a-chip” technology that weren’t optimized for existing workflows was not good enough for the rigors of the pharmaceutical industry, Caliper decided that it needed to integrate the chip into the lab. Caliper understands that customers have made substantial investments in existing infrastructure and that for new technologies to be adopted, they need to interface with that infrastructure. In July 2003, Caliper Technologies acquired Zymark Corporation. This combination bridged the interface between micro and macro fluidics. Caliper brought a detection platform with unprecedented data quality and experimental control. Zymark’s expertise in nanoliter liquid handling provided sample preparation solutions to feed the microfluidics platform and to interface with the existing microtiter plate architecture. Zymark also brought a seasoned management team with a history of developing real solutions for the pharmaceutical industry. The coupling of Caliper’s innovative technology with Zymark’s strong customer relationships and automation expertise has enabled the development of solutions that are ready to be deployed today.

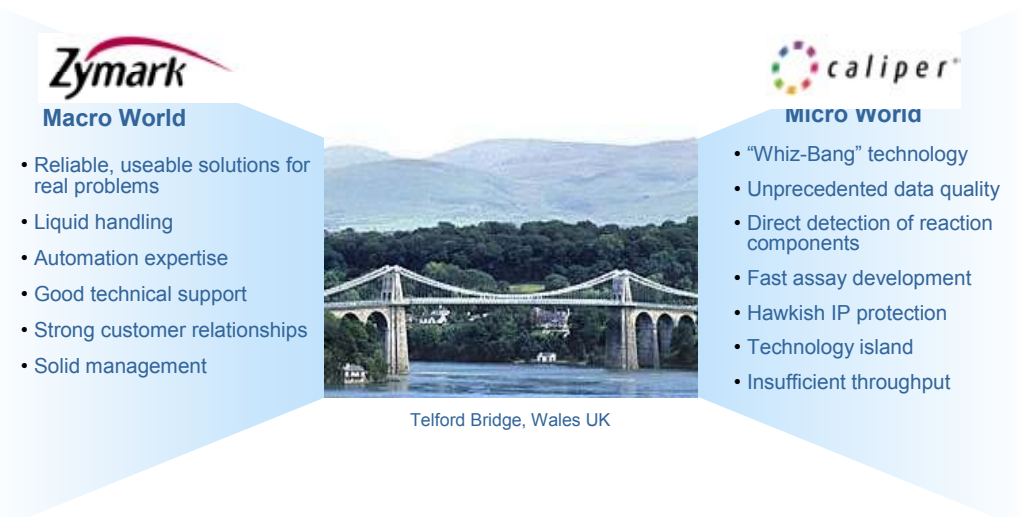


Figure 1. The combination of microfluidics and automation expertise enables Caliper Life Sciences to deliver high quality, reliable instruments.³

Caliper has realized that the promise of microfluidics is much larger than any one company can deliver. Previously, Caliper aggressively protected its intellectual property. Today, Caliper is working with others to establish microfluidics in a range of applications. Whereas previous microfluidics companies were technology islands, Caliper has realized the power of partnerships and has developed products with Agilent, Bio-Rad, QIAGEN, Affymetrix, and others. These partnerships are evidence of a systematic,

³ For a comprehensive study of the impact of microfluidics on drug discovery, see Kevin Hrusovsky’s keynote presentation for MipTec 2004.

standardized approach that is being employed to develop microfluidics-enabled solutions that are easily adopted into existing laboratory workflows.

The partnership between Caliper and Affymetrix is an example of the power that can be delivered through a collaborative approach. The two companies will develop products that leverage Caliper's expertise in high-throughput automation and microfluidics with Affymetrix' expertise in microarray technology and applications. The first products will automate GeneChip microarray target preparation steps including cDNA synthesis, purification, normalization, hybridization, washing, and staining for expression analysis. The automated system will enable a single operator to run up to 96 RNA samples at a time.

“We’re extremely pleased to partner with Caliper Life Sciences, a recognized leader in liquid handling automation and microfluidics, to provide robust industrial solutions and standardization of genomics processes. We view this as a critical next step in our goal of industrializing micro array technology to further increase efficiency and quality of results.”

Trevor Nicholls, Chief Commercial Officer, Global Operations at Affymetrix

Why Should I Look at Microfluidics Technology Today?

There are numerous benefits of this platform, not the least of which are better quality data, shorter assay development time, and versatility in the types of experiments that can be run.³ Because of the high quality data and the broad applicability of the technology, one of the most compelling benefits is the ability to standardize on one platform and achieve organizational advantages by performing experiments around the globe in a uniform, directly comparable fashion.

Features	Benefits	Applications
<ul style="list-style-type: none">• High Quality Data• Macro/Micro Integration• Digital Information• Integrated Sample Prep & Detection• Direct Measurement of Reactants• Short Assay Development• Versatile Platform• Low Reagent Usage	<ul style="list-style-type: none">• Standardization• Relevant Information• Decentralization• Organizational Knowledge• Change Management	<ul style="list-style-type: none">• Screening• Biological Assays• Lead Optimization• Proteomics• Genomics• Diagnostics

“We believe that Caliper has developed the right platform because it enables a direct measurement of activity. We no longer have to optimize two or three distal links between the biological event and the detection system. Because of the direct measurement and the high quality data generated by microfluidics, the Caliper technology is a platform we have adopted as a cornerstone of our discovery process.”

Bill Janzen, VP of Operations, Amphora Discovery Corp.

Exquisite experimental control provides unprecedented data quality

Are high quality data and high throughput experimentation two ends of a spectrum, or can they coexist in one platform? Many companies choose one or the other and focus their efforts at enhancing quality or improving speed, but rarely both.

“When we shifted from 96-well plates to 384-wells, we lost quality, and again when we shifted from 384 to 1536. We have a big library and we screen a large number of targets per year. The false results are moot because we have so many projects.”

VP of Chemistry, Drug discovery company in San Francisco, California

“I’ve done HTS with millions of compounds, and I’ve done focused screening with very high quality compounds. Not to disparage the HTS group, but if you look at numbers and sacrifice quality, you won’t be successful.”

VP of Preclinical Development, Biotechnology company in San Diego, California

The entire scientific method is based upon reproducibility. Data that is not reproducible is suspect. In the screening world, reproducibility is a luxury that few enjoy. Combinatorial libraries are considered good if they meet the 80:80 rule, which is to say that 80% of the compounds are at least 80% pure. In order to achieve reproducibility, variables need to be controlled. When scientific experiments are conducted in numerous locations around the globe, the disparate laboratory environments contribute additional variables, such as temperature, light, and humidity. Differences in laboratory environments, over time and among locations, negatively affect the reproducibility of experiments.

Caliper systems provide exquisite environmental control. Precise volumes of reactants are mixed uniformly. Evaporation is mitigated and temperatures are controlled. Each compound sees the same environment, generating reproducible results.

By eliminating variations in sample preparation, reaction conditions, and detection methods, the Caliper platform provides consistently high quality data. Aventis has adopted Caliper systems as a standardized platform because of the unprecedented data quality they have observed. With typical microtiter plate assays, CVs are in the range of 10 – 20%. Aventis has found that the raw data generated from Caliper instruments has a maximum CV of 5%, and the average CV is much lower.

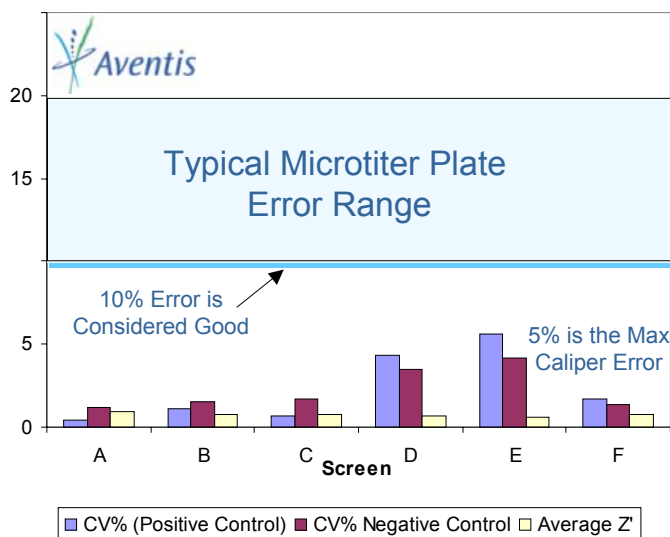


Figure 2. Microfluidics generates high quality data. Data courtesy of Aventis.³

“The key benefit is the unprecedented data quality we obtain using microfluidic technologies in a standardized platform.”

Dr. Kurt Stoeckli, VP and Global Head of Lead Discovery Technologies, Aventis Pharmaceuticals

Short assay development times

The amount of time necessary to develop initial biological assays can be as long as 6 to 9 months, which makes this step a substantial bottleneck in the discovery process. Long assay development times are common because optimal substrates need to be identified, reaction conditions need to be optimized, detection reagents must be titrated, and calibrations need to be developed. Using Caliper technology, many of these steps can be eliminated or shortened. Because the microfluidics platform provides direct detection of reaction components, there is no need to optimize the reaction for the detection reagents. This approach also allows experiments to be conducted without the added burden of having radioactive isotopes in the laboratory, or the need to find a high affinity, specific antibody for a particular assay class.

“The ability of the Caliper platform to directly measure substrate and product generates relevant data without compromise ... the Caliper platform accelerates lead generation because all of the data provides reliable information about activity.”

Marty Haslanger, CEO of Amphora Discovery

Indeed, there is no compromise between the optimal reaction conditions and optimal detection conditions. The direct measurement of reaction components enables facile calculation of percent turnover. Caliper has also created automated procedures for quickly identifying and optimizing substrates. In combination, these features reduce the assay development substantially.

“Given similar starting points, assay development with microfluidics is 50% faster than with traditional microtiter plate-based technologies.”

Dr. Aimo Kannt, Aventis Pharmaceuticals Lead Discovery Technologies

In house Kinase Selectivity Screening (KiSS)

Because assay development times are shorter, many customers have found that they can develop more assays. One key benefit is that kinase selectivity panels can be supported in house. These panels are important because they provide information about potential side effects, which is exactly the kind of experimental information that is needed to prevent late stage clinical failures. Many companies currently outsource kinase panels, which means they do not have experimental control and they cannot run as many samples as they would like. The costs of outsourcing are not inconsequential and can be as much as \$10,000 - \$20,000 per screen. In fact, many companies estimate that as much as 5% of the cost of a screening project is directly attributed to outsourced kinase panels.

Kinase Selectivity Screening Panel

PKA	CHK1	Svk
Fyn	C-TAK1	GSK3b
PKCa	PRAK	LCK
CK2	CK1	RSK1
AuroraA	PKD2	Flt3
Abl	P38a	ROKa
Akt1	CHK2	SGK
CAMKII	MSK1	FGFR3
IGF-1R	MET	MST2
PAK2	ERK2	
CDK2-cyclinE		MAPKAP K2

Microfluidics generates standardized, electronic results for numerous applications

The versatility and broad applicability of the microfluidics platform underscores the power of the technique. The Agilent Bioanalyzer 2100, which uses Caliper LabChips, provides researchers with the ability to perform numerous standard procedures, such as protein molecular weight determination, DNA sizing, RNA analysis, and cell sorting, all on an standardized instrument platform. The Caliper LabChip 90 provides the same

functionality as the Bioanalyzer 2100, but in an automated fashion. Both instruments provide high quality, electronic data in a format that is readily analyzed and shared.

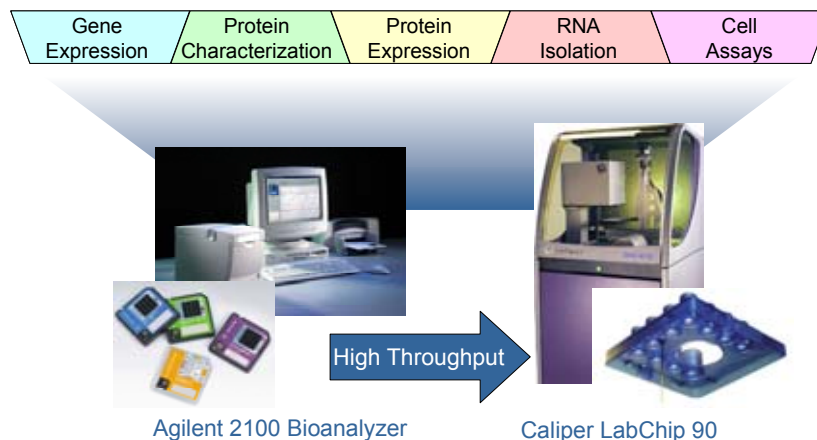


Figure 3. The Agilent 2100 Bioanalyzer and Caliper LabChip 90 are easy-to-use systems that provide digital, high quality data with reduced labor requirements.³

For high throughput screening applications, the Caliper LabChip 3000 provides the ability to perform screens of multiple targets on one instrument. Example target classes include GPCRs, kinases, proteases, ion channels, and lipid modifying enzymes. The walk-away functionality of the LabChip 3000 allows one scientist to operate three instruments simultaneously and generate more than 100,000 data points per day. Because the experiments are miniaturized, the reagent usage is substantially decreased, lowering the cost per data point. A typical high throughput screen of a library containing one million compounds would require 50 micrograms of highly purified protein. With a Caliper platform, the same screen would consume less than 1 microgram of protein.

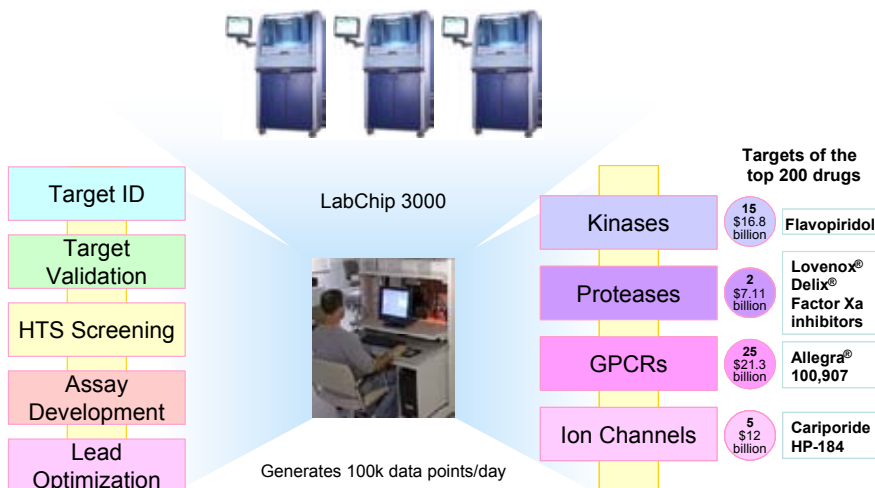


Figure 4. The Caliper LabChip 3000 is a standardized platform that allows direct measurement of reactants, reduced assay development time, exceptional data quality, economical throughput and reduced reagent usage.³

A Platform for Standardization

Within any given major pharmaceutical company, there are numerous functional silos generating different data from different technologies with different levels of error. The error is being generated from different assay formats, different supplier technologies, different researchers, and different experimental conditions. When all of these sources of error are added together, the resulting database becomes fraught with inconsistencies. Because of the lack of standardization, scientists become focused only on their silos; they understand and trust only the data that is generated by their teams. As a direct consequence, information is not shared within the organization and the innovation process is hindered.

“In the field of observation, chance favors only the prepared mind.”

Louis Pasteur

One way to create an organization of prepared minds is to have standardized technologies so that scientists can move among therapeutic areas or functional groups and cross-pollinate by sharing ideas. This standardization is achieved by having researchers use the same technology platform to conduct different types of experiments. However, standardization through centralization often results in additional bottlenecks. Decentralization is an essential component of innovation.

This is precisely what microfluidics can provide to the industry. This is a revolutionary development, not just in the way in which microfluidics is viewed, but also for the entire discovery process. Companies that have realized the power of this revolution – companies like Millennium, Amphora, Eli Lilly, Pfizer, and Aventis – have the ability to retool their discovery engines and have experienced significant organizational and scientific advantages.

The Caliper platform provides better quality data in an electronic format and allows shorter assay development times. Through Kinase Selectivity Screening (KISS), this platform provides more clinically relevant information about side effects earlier in the discovery process. This system confers the benefits of a standardized platform, without the limitations of centralized operations. A common interface and standard operating system also makes it easier to share information and adopt new techniques. Because of the broad application of microfluidic systems to genomics, proteomics, screening, and diagnostics, the Caliper technology is a platform for standardization that is deployable today.