

*'By establishing a common thread in the test tube and the animal, scientists can greatly increase their confidence that the results of both experiments are clinically meaningful.'*

# editorial



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## Getting on the critical path: better evaluation tools for drug discovery and development

### Better, faster, cheaper

Each decade, advances in technology and increasing globalization make it easier for companies across many industries to become more efficient. The computer industry is a good example – over the past couple of decades, tremendous technological progress and a trend toward outsourced manufacturing and service has enabled better and faster computer products to be delivered to the masses at increasingly low cost. However, the pharmaceutical industry has not fared as well over the past two decades. During the period between 1983 and 2003, pharmaceutical companies suffered through declining pipeline productivity and a rash of high-profile safety issues, yet the cost of R&D at these companies increased nearly 10-fold (Source: Frost & Sullivan).

One hypothesis for the cause of the pharmaceutical industry's productivity gap is that too much emphasis has been placed on

high-throughput low-cost *in vitro* experimentation testing. In an effort to speed the drug discovery process, little attention has been given to the quality or clinical relevance of data being generated. The advent of miniaturized high-throughput screening and combinatorial chemistry techniques led scientists to commit a larger proportion of resources to a brute force *in vitro* approach, with the hope that running many lower cost experiments in a short amount of time would allow them to increase their odds of finding the next blockbuster drug. The results, however, have been less than desirable and new approaches are clearly needed.

### The FDA's Critical Path challenge

The challenges pharmaceutical companies face have not escaped the attention of the FDA, who in March 2004 issued a report titled 'Challenge and Opportunity on the Critical Path to New Medical Products'. Their diagnosis was that although tremendous advances in basic scientific knowledge have been made, this knowledge has not translated into practical tools that enable the development of new medicines. As a result, the FDA proposed that 'the goal of Critical Path research is to develop new, publicly available scientific and technical tools – including assays, standards, computer modeling techniques, biomarkers, and clinical trial endpoints – that make the development process itself more efficient and effective and more likely to result in safe products that benefit patients.'

In March 2006, the FDA then issued its 'Critical Path Opportunities Report', outlining the ways in which the industry can begin to address these productivity and safety issues. Specifically, the FDA outlined distinct areas of research determined to hold the greatest potential to impact drug development productivity:

- Better evaluation tools
- Streamlining clinical trials
- Harnessing bioinformatics
- Moving manufacturing into the 21st century
- Developing products to address urgent public health needs
- Specific at-risk populations (e.g. pediatrics)

In addition, the FDA pointed out the need for an unprecedented collaborative effort among the academic research community, industry and scientists to tackle the specific projects in each of these categories.

## Better evaluation tools: the search for new biomarkers

The first topic in the Opportunities Report, Better Evaluation Tools, emphasizes the importance of biomarkers and new imaging technologies to help improve the productivity of drug discovery. These tools can help scientists perform more clinically relevant experimentation before a compound reaches clinical trials, therefore improving a drug's chance of making it to market.

Tools already exist to improve the relevance of preclinical experimentation. Microfluidics-based *in vitro* assays, for example, produce screening and profiling data that is much more meaningful than standard homogenous assays. Now, new imaging technologies are emerging – for example, biophotonic animal imaging that allow scientists to study the same biological system both *in vitro* and *in vivo*. By establishing a common thread in the test tube and the animal, scientists can greatly increase their confidence that the results of both experiments are clinically meaningful.

The threads that link *in vitro* and *in vivo* experimentation are biomarkers, which have arguably become the hot topic in drug discovery and development circles. The number of possibilities for potentially useful biomarkers is overwhelming, and much work must be done in order to identify, characterize and qualify them. Discovering sought after biomarkers can be a difficult and time-consuming process but the end result is worth the challenge.

## Case study: Pfizer's Sutent®

A recent example of the way that *in vitro* experimentation, *in vivo* experimentation and biomarkers interplay is found in the development of a promising new drug from Pfizer, Sutent®. Sutent was recently approved for two kinds of cancers: gastro intestinal stromal tumor and advanced kidney cancer. Using biomarkers, Pfizer was able to bridge *in vitro* and *in vivo* experiments to gain a much clearer understanding about the mechanism of action of Sutent® [1].

Early preclinical work with Sutent® included *in vitro* studies to directly measure the activity of the drug against vascular endothelial growth factor (VEGF; biomarker #1), which scientists believed was a good target for the cancers they were studying. From these experiments they determined that Sutent was a good inhibitor of this receptor *in vitro*.

Pfizer's *in vivo* experimentation on Sutent® used Xenogen's biophotonic imaging technology, which uses bioluminescence detection to measure biological systems that have been genetically altered to express the luciferase enzyme. Mice were injected with various classes of tumors expressing luciferase and, after the tumors were allowed to grow to a certain size, Sutent® was administered. Using bioluminescence monitoring, scientists were able to observe a cause and effect relationships between administration of the drug and tumor shrinkage (biomarker #2).

Although tumor shrinkage is an excellent biomarker, Pfizer scientists know that animal models are not always good predictors of human drug activity. To understand the results of this experiment better, they performed a histological evaluation of these

same mice. In mice treated with Sutent® they found a decrease in tumor microvessel density (biomarker #3), which was consistent with the drug being 'on mechanism'. This result indicated that Sutent® was shrinking the tumor by hitting the desired target receptor, VEGF, which is responsible for microvessel formation.

Pfizer scientists were able to use several biomarkers to paint a mosaic of the activity of Sutent® *in vitro* and *in vivo*. The results raised their confidence that their drug candidate was on mechanism and ultimately accelerated the approval process for this important new drug.

## Looking ahead

There are many reasons to be hopeful that we are starting to make progress towards better productivity in drug discovery. The latest study out of Tufts Center for the Study of Drug Development [2], showed that in the period 2003–2005 the number of new drugs that were entering clinical testing jumped 52% compared with the period 1998–2002. This statistic, coupled with the fact that the percentage of drugs that make it through to market remained at ~20%, indicate that the productivity gap might be closing.

Although biomarker research is in its infancy, the Sutent® example illustrates its potential. This exciting work and the growing use of imaging technologies – such as biophotonic imaging – will play a key role.

Maintaining an industry-wide commitment to collaborative Critical Path research is important – biopharma companies, tool manufacturers and academia must work together to make the needed progress. At Caliper, our strategy and product development plans are driven by the need for high productivity preclinical experimentation technologies with greater clinical relevance. We are exploring techniques to make *in vitro* and *in vivo* experimentation technology more correlated, productive and clinically relevant by using our vast estate of microfluidics, automation and, through the acquisition of Xenogen, our biophotonic imaging technologies. In this way, we are working closely with our pharmaceutical, biotechnology and academic customers, in alignment with the FDA Critical Path Initiative, to actively participate in bringing much needed improvements to the drug development process and to human health.

## References

- 1 Mendel, D.B. *et al.* (2003) In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin. Cancer Res.* 9, 327–337
- 2 Tufts Center for the Study of Drug Development Impact Report (2006) New drugs entering clinical testing in top 10 firms jumped 52% in 2003–05. *Analysis and Insight into Critical Drug Development Issues*, 8, Tufts University

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