



Integrating the Science and Technology Revolutions

There's no question that technology influences drug development, and that innovation is one of the driving forces behind improved health worldwide. How will new science and technology change healthcare? What does the future hold for the pharmaceutical industry?



Anthony J. Sinskey^{1,3}, Stan N. Finkelstein^{1,2} and Scott M. Cooper¹

¹Program on the Pharmaceutical Industry (POPI), ²MIT Sloan School of Management and ³MIT Department of Biology, Cambridge, MA 02139

In this, our first in a series of columns in *PharmaGenomics*, we're going to take a closer look at several technologies that need to be integrated into pharmaceutical discovery and development. We're also going to explore the implications of these technologies for the pharmaceutical business as a whole. And we present a model for realizing the promise of pharmaceutical innovation.

Current Climate

Let's look at the business picture first. Statistics tell an interesting story. During the last four years, a tremendous drop-off in the number of new chemical entities (NCEs) launched has occurred – a trend that, with few exceptions, began in the early 1990s. Meanwhile, R&D expenditures steadily continue to increase by several billion dollars annually (1). These dynamics have been accompanied by data confirming the hypothesis that pharmaceutical firms are terminating the development of unsuccessful compounds more quickly, which changes the approval rates for investigational drugs (2). At the same time, the number of top 100 pharmaceutical products

scheduled to go off patent by 2005 has increased greatly (3).

Meanwhile, both spending on prescription drugs and the percentage of healthcare costs attributable to prescription drugs rose throughout the 1990s. Part of the increased spending has come from increased demand for drugs, especially new drugs, supported by increased drug coverage in healthcare plans. This has occurred partly because drugs offer the benefits of longer life and improved quality of life, and thus help to reduce overall healthcare expenditures through the avoidance of costly hospitalizations.

The current business context, then, is one of tremendous pressure on the major pharmaceutical firms: just as they are losing or about to lose patents on their strongest performers, they face slowing growth and declining R&D productivity. In essence, they are spending more money to develop fewer products, and this comes at a time when the market demands continued and greater innovation. Furthermore, while the rewards must be large to justify the risk involved in massive R&D expenditures, blockbuster drugs that can pay back those investments are rare,

indeed — less than 4% of all pharmaceutical products generate sales of more than \$500 million (4).

The scientific context is no less daunting. As those of us associated with the pharmaceutical community often hear, "All the easy drugs have been done." New drugs for more difficult diseases such as cancer, diabetes, sepsis, multiple sclerosis, autoimmune disorders and numerous infectious diseases are on the agenda, but questions abound. Will the post-genomic era lead to effective treatments for such complex diseases? What enabling science and technology platforms will be required? And what can the industry do to meet the challenges involved in these drugs' development?

Integrating Technologies

Important paradigm shifts are on the landscape of drug discovery, as advancing technological capabilities are employed. We have moved beyond "random" drug discovery, where compounds are screened based on whole or partial animal screens. "Randomness" has given way to mechanism-driven drug discovery, where screening is performed against a specific known or suspected mechanism, as well as to fundamental science discovery. Still, the numbers suggest that much more must be done. No single technological advance is sufficient to lead to an innovative pharmaceutical product.

Despite the drop in NCEs launched, an unprecedented

The data from genomics, proteomics and other high-throughput data-gathering technologies **have to be converted** into medically relevant knowledge.

number of NCEs is available to investigate, thanks in large part to the biotechnology revolution and the advances it has spawned in biology and combinatorial chemistry. We have at our disposal many important new technologies for investigating complex biological systems, for measuring drug effects and for predicting outcomes. Scientists working in drug development are focusing on unraveling cell pathway networks, and are using protein and molecular interaction maps to refine the understanding of human disease pathogenesis.

However, the goal of greater human health will not be served effectively by this revolution without a convergence, or integration, of technologies. Such integration would hold the first key to the pharmaceutical community's ability to exploit the many opportunities that exist for drug development. The second key will be to translate the vast information that can be obtained into medically relevant knowledge.

Information is the currency of innovation. The increasing availability of relevant biomedical knowledge is paving the way for the future of drug development. New scientific techniques — genomics being perhaps the most familiar — and technological advances are making it possible to acquire the information necessary to create working mathematical models of protein and gene functions in cell path-

ways, cell-cell interactions, tissue and organ coordination and, ultimately, in an entire human being. The technological accessibility of systems biology, made possible by this information and the informatics tools to manage and apply it, is the basis for developing innovative drugs. The biotechnology revolution puts us on the cusp of developing improved medicines to address unmet medical needs, including those needs that have yet to be recognized. These scientific advances will improve drug efficacy, ensuring more reliable patient response to therapies. Improved drug safety and reduced side effects also are promised.

Scientists in academia and in pharmaceutical laboratories have learned that investigating complex systems leads to significant returns of knowledge. The greater the complexity of the system, the greater the knowledge return. We've advanced from looking at gene sequences and pharmacophore information to a significantly greater understanding of pathogenesis. This has taken scientists deep into examinations of symptoms (the body), pathology (organs and tissues), biochemistry (cells) and mechanisms (molecules).

It is critical, however, to understand that the major challenge for scientists and the pharmaceutical industry is to integrate effectively all the technological advances. This is what will yield the return. Once acquired, the data from genomics, proteomics and other high-throughput data-gathering technologies have to be converted into medically relevant knowledge — that is, into an understanding of the complex systems that underlie cell physiology. Only then can the knowledge be applied successfully to improved productivity in drug development.

Rejuvenating Pipelines

MIT has undertaken a major initiative in network biology that represents the ways the pharmaceutical industry needs to transform its drug discovery and development efforts. The initiative, which involves faculty from The Program on the Pharmaceutical Industry (POPI), seeks to exploit the knowledge base at the interface of biology and engineering. It involves network-based mapping and modeling of signal transduction pathways to understand biological decision processes and distinguish normal and diseased states. In the area of tissue engineering, it involves the design of cell-based sensors and devices for pharmaceutical development. In the area of molecular toxicology, it involves mechanistic analysis of cellular homeostasis, DNA damage pathways and processes that maintain genome integrity. Further, in the area of molecular oncology, it involves linking genotype and phenotype in the molecular analysis of oncogenes, tumor suppressors and mutators.

Chemical engineers at MIT are saving time through microsystem technology. They are expanding the scope of microfluidic tools for small molecule chemistry that could further revolutionize chemistry research and production. Parallel, combinatorial analysis using small amounts of expensive reagents will enable engineers to help accelerate the drug development process. Signal transduction pathways also need to be unraveled to explain functions within a cell; this holds the promise of better identification of functional targets for pharmaceutical intervention.

These advances, coupled with many others, promise to strengthen the pharmaceutical industry at a time when it seems that the pipeline is running dry.



The better measurements enabled by advanced technologies will lead to better decision-making in drug development, and more prolific pipelines. Novel therapies will find a way to the public faster — resulting in obvious health benefits. The knowledge base in molecular medicine is growing rapidly, and with the increased understanding of complex biological systems this affords — along with increasingly reliable computational models for predicting outcomes — society is approaching healthcare that anticipates disease states rather than merely alleviating disease symptoms.

The compounding nature of technological change and innovation calls for consistent and committed financial support. The question of where these resources will be found must take into account legitimate concerns beyond those of the drug companies themselves, including drug access, high prices and variable prices across borders. Further, its answer requires paradigms that are not yet in place. Policy-makers and industry will need to work together, worldwide, to address the challenges.

Policies and Scientific Perspectives

In forthcoming issues of this journal, we will explore the policies that can help foster the coming wave of innovation, and will offer a scientific perspective on them. In our next column, we examine protein microarray technology — which, like all of the new technologies we will look at, underscores the importance of “network biology” to the future of innovative drug development. This exciting advance allows the simultaneous analysis of thousands of parameters within a single experiment and already has demonstrated applications for enzyme-substrate, DNA-protein and differ-

ent types of protein-protein interactions. In biomedical research, protein microarray technology enables scientists to analyze in parallel all the relevant diagnostic parameters of interest. The potential acceleration of immune diagnostics is significant.

References

1. IMS/PriceWaterhouseCoopers data.
2. J.A. DiMasi, *Clinical Pharmacol. Ther.* **69(5)**, 297-307 (2001).
3. IMS/PriceWaterhouseCoopers data.
4. Lehman Brothers PharmaPipelines Report, 2000. **PG**