The Coming Paradigm Shift in Pharmaceuticals

Pharmacogenomics holds the promise of more effective and better-tolerated therapies, which, in turn, mean more efficient use of healthcare resources. But there are many hurdles on the way to the pharmacy of the future.

In the business world, language comes and goes as swiftly and regularly as a Times Square-Grand Central shuttle train in the New York City subway system. Usually, after a short time, words and phrases begin to lose their resonance — which is unfortunate because this happens from overuse and not because the meanings are inaccurate. All this is by way of apology for using “paradigm shift” in the title of this month’s column. Perhaps we should have used “revolution,” but that’s also a bit worn out.

Semantics notwithstanding, the changes on the horizon for the pharmaceutical industry are of epic proportions (whoops, another overused phrase). A transition soon will be underway — indeed, at some firms it has begun already — and the science of pharmacogenomics is at the center of it. The big questions are: What does this mean for pharmaceutical R&D? What will the new business model look like? Who will get ahead of the curve, who will be forced to change and who will not survive?

In this, the first of a two-part column, we will explore the coming paradigm shift and the opportunities it presents for the future of pharmaceuticals. In one sense, we’re heading toward a description of the pharmacy of the future. But to get there, we’ll need to explore how systems biology, about which we have written previously in these pages, can be translated to the healthcare industry. We also need to explore issues of economic viability.

An Old Business Model for New Science?

Today’s pharmaceutical firms employ a business model that has served them quite well for decades. At every major firm, the straightforward formula essentially is the same: develop a highly successful blockbuster drug (at a cost estimated between $450 and $800 million), reap enormous profits (justified by the tremendous investment made in R&D) and reinvest a good portion of those profits to fuel the discovery and development of new (ideally, also blockbuster) drugs.

Let’s put aside for now whether or not that’s an appropriate model, and consider the cost. Why does it cost so much to develop drugs and bring them to market? The answer has everything to do with why the paradigm shift is coming.

The pharmaceutical industry speaks of drugs as being “in the pipeline.” Figure 1 represents that pipeline. During the first stage, drug development, the costs, scientific complexity and time requirements involved are staggering. Applied research — including synthesis, biological testing and pharmacological screening of up to 10,000 compounds — takes up to four years. The number of compounds is narrowed down to perhaps three, and clinical development takes another eight years, including Phase I, II, and III clinical trials. It can take two or three years to register a drug and plan for the market launch.

The product is then ready for market, but the cost has been borne and the complexity has symbolically been reduced from 10,000 compounds to one useful drug.

But were those 14 years a prelude to market success? Alas, the fun is only beginning. As Ned McCulloch of IBM Life Sciences asks, “Can life sciences products get to patients (1)?” At the other end of the pipeline, the new drug — approved and ready for market — faces a set of hurdles that add new costs and additional complexity. There’s the issue of coverage and reimbursement. Who will pay to buy the new product? Physician acceptance and training must be considered. The health system infrastructure must be addressed to ensure that there is clinical decision support for diagnosis and prescribing.

And finally, will patients accept and use the new drug?
The prospect of success would appear daunting under this traditional scenario, but with blockbuster drugs and the billions of dollars in sales that such drugs represent, the pharmaceutical industry has done well for itself. And in doing so, patients have been assured of R&D that keeps leading to “better” therapies.

We struggle to see any way in which the old business model has much of a chance with the new science. As one of our colleagues has so poignantly put it, “The easy drugs have been done.” On top of this, “precise diagnoses leading to universal specific treatments are, for many illnesses, myths (2).” Many of the “easy” drugs our colleague speaks of have, or are about to, come off patent. And the next generation of drugs might not be anything like blockbusters, but more like what this same colleague calls “druglets” that address, with better effectiveness, the unmet medical needs of ever smaller segments of the population.

And therein is the change being ushered in by the new science.

A Future of ‘Druglets’?

We stand on the cusp of a new world of pharmaceuticals. Doctors and scientists know that whether or not a patient benefits from a prescription drug is a function of the individual’s genetics, the drug and the disorder or condition for which the drug was prescribed. Changes in science, technology and clinical medicine afford a better understanding of these determining characteristics at a molecular or sub-molecular level. This holds a great promise: the discovery of more effective and better-tolerated therapies means more efficient use of healthcare resources.

From a business perspective, this changes everything. If the future is one in which correlation of drug response with individual genotype is the norm, it will mean that drugs that would be unsafe or ineffective for a given patient will not be prescribed. It would also open the possibility of marketing the druglets.

An article in a recent issue of Health Affairs describes this new environment as well as we could have: “In the long run, [this] could undermine the current focus on blockbuster drugs that bring in large annual revenues for the life of a
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drug patent. Although this pattern is likely to continue for some time, and segmented markets already exist for many drugs, the emergence of large variation in the genetics of drug response could divide demand for pharmaceuticals into increasingly smaller subgroups, each with its own unique [pharmacogenomic] needs. Prescribing drugs according to genotype could reduce demand for particular drugs, thus lessening the stream of revenue and the profits available to invest in research and development...Unless more new drugs coming on the market offset that reduction, [this] could increase market differentiation, reduce profits and perhaps effect change in investment patterns and the scope of industry-funded research (3).

Pharmacogenomics and Medical Practice

That being said, it doesn't seem at all hyperbolic to suggest a paradigm shift or even a revolution. But does the pharmaceutical industry have to respond with a shudder?

We think not. We believe that pharmacogenomics already is pointing the pharmaceutical industry in the right direction, where business opportunities still exist and pharmaceutical firms can thrive. For instance, knowledge of individual genetic structures and variations among them on a molecular basis is leading to defining targets based on pharmacogenomics. This could lead to more systematic searches for lead compounds that address these targets. In our last column (July/August 2002, PharmaGenomics, p. 24), we wrote about how protein microarray technology allows the simultaneous analysis of thousands of molecular parameters with a single experiment. That is an ideal example of the promise of new science and technology.

The next steps for the healthcare industry, broadly defined, are to work out how to change medical practice so that a pharmacogenomics-driven pharmaceutical industry makes sense for practitioners and businesspeople alike. We know that one of the principal challenges involves pharmacogenetic testing. As the Health Affairs article explains, “The pace of integration of [pharmacogenetics] into medicine will also depend on medical and social acceptance of a greatly increased use of genetic testing in the healthcare system. Actors at every level in the system will have to learn to approach many diseases and drugs in [pharmacogenetic] terms.”

Such tests will have to be valid, accurate and verifiable. Providers will need to understand how to interpret the tests properly, and when to prescribe whatever druglets are indicated. More importantly, they will have to be embraced as a positive development, not one that frightens patients concerned about genetic privacy, discrimination and their civil liberties. These ethical issues speak to the complexity of the problem.

Getting There From Here

We think pharmacogenomics holds an additional promise: somewhere in the new science and technology are some of the answers to the challenge of translating systems biology to the healthcare industry. While it might involve new strategies for disease management, we are sure it means new types of patient-physician interaction.

The science of pharmacogenomics is real, and its opportunities for societal benefit are great. But how can we get through the inevitable transitional period to transform the business of pharmaceuticals such that the opportunities can be captured? What will lead to acceptance of making therapeutic decisions based on pharmacogenomic factors and employing pharmacogenomic therapies?

Part two of this column, in the next issue of PharmaGenomics, will explore the role of pharmacogenomics in mitigating some of the hurdles we described earlier that are faced by new drugs on the market. We will present some models that we think can help frame the vital discussion just beginning to unfold. Our aim is to help ensure that a paradigm shift doesn't mean the ground shifts beneath the feet of pharmaceutical researchers to such a degree that the potential for new and better therapies falls into a hole.

References

3. J.A. Robertson, B. Brody, A. Buchanan et al., Health Affairs 21(4), 155–167 (July/August 2002).