To make better therapeutics, companies strive to increase the content of results and get them faster.

The Tools of Change in Big Pharma

By Michael Szpir

In the jungle of the marketplace, the pharmaceutical industry is now experiencing enormous pressures to evolve into a different kind of animal. In 2004, the U.S. Food and Drug Administration (FDA) reported that the annual number of new drugs and biologics submitted for approval dropped from 97 to 40 between 1993 and 2003, even though spending on research and development increased two and a half times during the same period. Similar developments have been seen at regulatory agencies around the globe. Such trends threaten the extinction of big pharma as we know it.

People in the industry feel the pressure coming from all quarters. The withdrawal from the marketplace of widely used drugs, such as Merck's Vioxx® (Whitehouse Station, NJ), because of health risks has heightened public concerns about drug safety. Add to that the growing expectations of shareholders for greater profits, and there's little doubt that something must change in the business of making new therapeutics.

"The challenges for the pharmaceutical industry are mounting, and we don't see an end to that anytime soon," says Barry Springer, vice-president of enabling technologies at Johnson & Johnson Pharmaceutical Research & Development (J&JPRD; Raritan, NJ).

Among those challenges is the need to bring drugs to the marketplace faster than ever before. It now takes about 10 to 15 years from the time a company files an investigational new drug application with the FDA to reach final regulatory approval. Just about everyone thinks that's unacceptable. "There are some diseases that aren't being met with good medicines, so there's a real patient need out there," says Springer.

Steve Projan

And, of course, the longer it takes to produce a drug, the costlier it is. The Center for the Study of Drug Development at Tufts University (Boston, MA) estimates the cost of bringing a new therapeutic to the market at about \$948 million (in 2003 dollars). "Time is the most precious commodity we've got," says Steve Projan, vice-president and head of biological technologies at Wyeth (Madison, NJ). "The patent clocks are ticking while we do clinical trials—with a \$365 million-dollar-a-year drug, you lose a million dollars every day you don't get that drug on the market," he says.

So what is big pharma doing about all of this? For one thing, the industry isn't sitting back hoping that some new technology will come around the corner to save them. "The bloom has gone off the rose of buying the next *new* thing—the technology that is going to wipe everybody else out," says Bob Clark, director of the Informatics Research Center at Tripos (St. Louis, MO).

Bob Clark

Instead, industry leaders are taking a hard look at some of the technologies already on hand. "Although we're always looking for new technologies, a lot of our focus is to take existing technologies and push them as far as we possibly can," says Springer. The future of the industry hinges on where they do the pushing.

It Takes a Village to Create a Drug

Big pharma is starting to appreciate that *how* the technologies are integrated into the drug-discovery process is key to getting the most out of them. "It used to be data, data, data," says Clark, referring to the mountains of data generated by high-throughput technologies. "Now, it's info, info, info." People nowadays recognize that they need to share information, rather than just generate more data, Clark says. Indeed, Tripos has been working with Bayer (Pittsburgh, PA), Bristol-Myers Squibb (New York, NY), and Wyeth Pharmaceuticals to develop software to do just that.

As a result, there's a shift toward bringing people together into interdisciplinary teams, rather than isolating scientists like factory workers who toil independently on different aspects of drug discovery. "Several new research centers have all the different groups in the same building, rather than, say, having one building for biology and one for chemistry," says Clark. "Companies now recognize that discussions over cups of coffee are extremely valuable," he adds.

Schering-Plough (Kenilworth, NJ), for example, has implemented a systematic method of bringing together key stakeholders from drug discovery, development, manufacturing, and marketing, according to Thomas P. Koestler, president of Schering-Plough Research Institute. "We integrate a diversity of input into our decision-making process," he says. "We listen to the assessments of marketing experts as

Thomas P. Koestler

promising compounds are discovered; we involve manufacturing colleagues early in the clinical trial-development cycle, as well as our researchers, clinicians, and colleagues from distribution," he adds. The goal, he maintains, is to focus their energies on the most effective ways to bring a valuable drug to market, and to learn early in the process whether a compound is viable for continued work.

That's consistent with the views of Ramon Felciano, chief technology officer and vice-president of research at Ingenuity Systems (Redwood City, CA), who says that companies are trying to streamline their processes and reduce the costs of their failures by failing early. "While there are a large number of technologies and solutions, we are consistently seeing our customers invest in better solutions for sharing knowledge across their drug-discovery efforts," he says.

According to Felciano, this manifests itself in everything from better analytic and collaboration tools to full-scale knowledge-management solutions and "Google-like" portals for internal enterprise search. "Pharma customers have realized that unlocking and accessing internal knowledge, and linking that to what is known in the literature and in the public domain, enables them to design and implement more effective experiments and pursue new compounds with higher confidence," he says.

Looking Into the Crystal Ball of Pharmacokinetics

The need to know early in development whether a drug is going to fail means that making predictions about the potential toxicity of a compound, and determining whether the compound will be efficacious, are high on the list of priorities in the industry. Unfortunately, these needs and expectations have yet to be fulfilled. "One of the lessons from the biopharmaceutical industry in the past decade or so has been that a lot of our models haven't been as predictive as we would like," says Joe Miletich, senior vice-president of research and development at Amgen (Thousand Oaks, CA).

Toxicologist Katya Tsaïoun, president of Aprelica (Watertown, MA), thinks that part of the problem is that the field of toxicology is so enormously complex. "When you take an oral drug, the whole proteome of your body reacts; short-term gene expression changes, and many pathways become altered. Some of these changes have a therapeutic effect, and some have a toxic effect," she says. For that reason, fields such as toxicogenomics aren't ready for "primetime," according to Tsaïoun. "We're still in an information-gathering phase," she says.

Katya Tsaïoun

At Amgen, the scientists are spending more time studying medicines in people and the samples they collect from people, according to Miletich. "The challenge is that you can't control as many variables as you can in the laboratory, and you must

collect the information safely and ethically from human subjects," he says. "So we have to be very clever about how we do this, using the new technologies like imaging, arrays, and proteomics."

There's a similar trend at J&JPRD, according to Springer. "A lot of emphasis has been placed on biomarker discovery and molecular imaging," says Springer. Part of that is finding better ways to make measurements of what drugs are doing once they're in clinical trials. "Things go up and down in disease," he explains, "and what we're looking for are biomarkers that go up and down, and see whether they're consistent with the course of the disease, and the potential target of interest that might be associated with the disease."

Tina Settineri

The importance of biomarkers to the drug development pathway has been on the rise in the past few years, concurs Tina Settineri, director of pharma programs at Applied Biosystems (Foster City, CA). "Biomarkers are used throughout the entire drug-discovery continuum—from target identification, through cell and animal studies, to the transition into human subjects," says Settineri. Biomarkers have been especially important when it comes to making earlier "go/no go" decisions, for example, with toxicology biomarkers, and for reducing attrition rates during phase II and III trials, according to Settineri.

The emphasis on human studies corresponds to a more aggressive use of translational medicine at many pharma companies. "Wyeth has established a major translational medicine research

collaboration with Scotland—the entire country—including four major medical universities and the National Health Service,” says Projan. Initially, the collaboration is focused on defining the molecular basis of a disease. “So it’s not, ‘you have a fever,’” he says, “it’s ‘you have elevated cytokines—why do you have elevated cytokines?’” Projan believes that understanding a disease from a molecular point of view will translate into the best therapeutic approach for treating that disease.

Of ‘Omics and Systems

By most accounts, the ‘omics revolution, which was supposed to provide the technologies that would make drug discovery and development “faster, better, cheaper,” has not yet lived up to its promise. “Over the past few years, biologists have realized that statistical analysis of ‘omics data alone isn’t sufficient to get researchers to the actionable insights and decisions needed to drive the discovery process forward,” says Felciano.

Felciano believes, however, that the next generation of analysis tools will allow drug-discovery companies to take advantage of their investments in ‘omics. Pathway analysis, for example, can be used to determine how genes involved in a particular toxicity pathway are perturbed, which plays a key role in predicting the potential toxicity of a drug before much time and energy is invested. Big pharma is starting to invest in tools that help researchers to understand and examine their data in a comprehensive biological framework, according to Felciano.

That thrust into systems biology—understanding how a molecule behaves inside the whole animal, not just in the test tube—may be key to pharma’s future, according to Clark. “Somewhere between 30% to 50% of drugs that fail in clinical trials do so because of a lack of efficacy; in theory they should work, but for some reason they don’t in the system,” he says. “It’s a huge problem, and pharma must untangle all of this if they are to find new drug targets, too.”

Francisco M. De La Vega

Systems biology may also have an impact on the future prospects of personalized medicine, according to Francisco M. De La Vega, scientific fellow and senior director of computational genetics at Applied Biosystems. “Systems biology may help us to understand the relationship between the genetic variation seen in individuals, his or her susceptibility to disease, and the pathways the genes are involved in,” he says. “The goal is to identify ‘drug-gable’ genes that can be targeted for drug development.”

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De La Vega and his colleagues have been developing genotyping assays for drug-metabolizing enzymes, which could be used in the drug-development process. “The idea is that some of the genes could be used to stratify populations for clinical trials or to find indications that drugs could be useful for a certain patient population,” he says. The problem, according to De La Vega, is that it’s been very difficult to develop reliable assays for some genetic variants that are involved in drug metabolism.

De La Vega also believes there’s been too much hype about when and how the next generation of sequencing technologies will transform pharmacogenetics and personalized medicine. “These technologies involve high-throughput sequencing, but they are still far away from being able to directly impact the treatment of patients because the instruments and protocols are not simple,” he says. “The next generation is definitely going to advance the study of disease, but we will need to wait for yet another generation of sequencing technologies to have an impact on the treatment of individual patients.”

— **Michael Szpir** is a freelance writer based in Apex, NC.

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