**Productivity Counts—But the Definition Is Key**

With costs soaring, every company says it’s becoming more efficient. But what exactly does that mean?

For all but a tiny fraction of big pharma scientists, their work isn’t really about discovering new drugs to cure disease and improve human health. It’s about looking for druggable compounds: molecules that might bind to targets that could block or enhance a biochemical process that leads to a particular pathological state or impairment. And success isn’t measured by how much they have contributed to a drug or therapeutic medicine on the market. Rather, it means “hitting your numbers,” that is, achieving a preset goal of “deliverables”—be they compounds, animal data, or patients—that argue for moving along to the next step in the process.

Trouble is, that approach is hugely inefficient. The current cost of discovering and developing a new drug may be as high as $1.9 billion, according to an extrapolation by Joseph DiMasi of the Tufts University Center for the Study of Drug Development in Boston, Massachusetts, whose 2001 report pegging the number at $802 million was based on medicines that entered clinical trials as long as 20 years ago. Lowering that number is the current Holy Grail of the industry. “Productivity is our biggest challenge and the number one topic of conversation among my colleagues,” says Steven Paul, president of Lilly Research Laboratories and the top scientist at the Indianapolis, Indiana–based drug giant.

But consensus on the goal doesn’t mean agreement on how to get there. Big pharma management features a multiplicity of organizational models, all aimed at achieving greater efficiency. Some companies such as Pfizer are highly centralized, whereas others pride themselves on having small, semi-autonomous units. “Pfizer is probably at one end of the spectrum. Everything related to drug discovery has to go through either New London [Connecticut] or Sandwich, U.K.,” says industry analyst Roger Longman, co–managing partner of Windover Information Inc. in Norwalk, Connecticut.

At the other end, he notes, is U.K.-based GlaxoSmithKline (GSK), second in global pharmaceutical sales to Pfizer. Under the leadership of research chief Tachi Yamada, GSK has created Centers of Excellence in Drug Discovery around the world in six therapeutic areas, plus one center for biologics. Each has its own budget and hiring authority. “I wanted them to be small, and studies show that you can know the names of 300 people but no more,” says Yamada. The centers “have total control of their budgets and hiring. But they still have targets.”

Falling somewhere in the middle is a “hub-and-spokes” system that Roche follows. It allows its corporate headquarters in Basel, Switzerland, to keep tabs on research sites in the United States, Europe, and China. And although that arrangement can mean 2 a.m. teleconferences for Bob Stein, who oversees 1100 people at Roche Palo Alto, California, he says it’s vastly preferable to having “one big R&D operation that, like a 10-foot spider, has outgrown its body plan.”

There are also many views on which metrics are the most meaningful, and if metrics can even take you where you want to go. One popular view, espoused by Pfizer CEO Hank McKinnell and others, embraces “shots on goal.” That’s the belief that more compounds going into clinical trials translates into more successful outcomes and, ultimately, more marketable drugs.

But what kind of shots are most important? For Yamada, the key metric “is not the number of targets validated, or the number of chemicals selected. It’s proof-of-concept in patients.” His counterpart at Novartis, Mark Fishman, puts it even more bluntly. “[A drug candidate] is not a success until we’ve treated a patient with it.”

At New Jersey–based Wyeth Pharmaceuticals, which sits on the centralized end of the management spectrum, R&D president Robert Ruffolo has done a scientific analysis of the science of drug development. A 55-year-old pharmacologist and 28-year industry veteran, Ruffolo likes to say that “we’ve got numbers on everything.” And since coming to Wyeth in 2000, Ruffolo has probably gone further than any other pharma honcho in trying to quantify what his researchers should accomplish at each stage of the process.

“Some people say that they can pick winners,” Ruffolo told a meeting of pharma scientists gathered this spring in Washington, D.C. “But I believe that it’s still a crapshoot. I can’t pick winners, and after 30 years in this business, I haven’t met anybody who could.”

What Ruffolo can do, he says, is ride herd on the factors that he can control. Hence his insistence on production targets that take attrition into account and, if met, would allow for a sufficient flow of new compounds through the pipeline. Raising goals are based on achieving the goals, and it’s all computerized.
The magic numbers for Ruffolo are 12, 8, and 2. That’s a three-link chain of the annual number of compounds entering development, the number of investigational new drugs entering clinical trials each year, and the annual number of new drug applications submitted to the U.S. Food and Drug Administration. He says that his approach has helped turn around what he calls the company’s “pathetic” track record of submitting new drug applications in the years before he arrived. And best of all, it’s proven to be sustainable: Wyeth has met the targets every year since 2001, he says. “That’s the most important point. It’s a steady-state model.”

Ruffolo admits that approach didn’t win him any popularity contests at Wyeth. “Scientists hate this approach,” he says. “When I was a scientist, we used to say that you can’t manage science. But it needs to be.” Those who didn’t buy into the approach left the company, he says—and those who have remained appreciate knowing where they stand.

Richard Scheller takes a very different approach as executive vice president of research at Genentech, which has eschewed large acquisitions and does all research at its ever-expanding South San Francisco, California, campus. A neuroscientist and former Howard Hughes Medical Institute investigator at Stanford University, Scheller came to Genentech in 2001 after deciding that its culture meshed with his own philosophy of doing science. Genentech’s corporate strategy, labeled Horizon 2010, does include research goals for its more than 600 scientists over the next 5 years. But although they specify the number of new products to be moved forward for each of the company’s three major therapeutic areas, some goals omit key steps in the process. And they aren’t linked together in a formal manner.

Sitting in a top-floor office overlooking San Francisco Bay—and the pier that was allegedly the favorite fishing hole of co-founder Herbert Boyer—Scheller describes an ongoing study of Genentech’s attrition rate and the nature of its pipeline in a way that suggests he doesn’t view it as quite the priority that Ruffolo does. “It turns out that different types of projects fail for different reasons,” notes Scheller, who says that he “doesn’t know very much about big pharma” despite the fact that, based on the value of its stock, Genentech is the fifth-largest drug company in the world.

“For example,” Scheller says, “I’m expecting small-molecule throughput rates to be lower than for protein therapeutics. I’m also leading a project to understand the bottlenecks. And I think that they will turn out to be what you’d expect: Some projects will be underresourced, some will suffer from poor internal communications. When we’re finished, we’ll react appropriately. But I suspect that when we fix one problem, some other bottleneck will appear.”

Don’t be fooled by that dispassionate tone, however. Scheller isn’t afraid to be just as hard-nosed as Ruffolo in assessing the performance of his troops. But he doesn’t plan to do it from a spreadsheet. Knowing how to maintain a healthy pipeline, he says, “is more or less a matter of intuition.” And the most important thing about dealing with scientists, he says, “is to be clear about the reasons for your decision [for killing a project or shifting resources]. I’m not always going to be right. But I’ve earned a lot of respect from my credentials at Stanford and my achievements as a scientist.”

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