# Glass houses

*While regulators slow progress, pharma can also find fault within.*

BY RANDALL C. WILLIS

Health care costs are eating an ever-increasing portion of many countries' gross domestic product, and pharmaceuticals represent 10–20% of this pie, Robert Ruffolo, president of R&D for Wyeth, told his audience at the recent World Pharmaceutical Congress in Philadelphia. But overall health care expenditures and the percentage arising from pharmaceutical endeavors can be controlled, he said, if everyone is willing to pull their weight in improving the efficiency of the drug discovery process.

## Ground state

Simply throwing more money at the problem has not alleviated the situation, Ruffolo argued. Unlike most industries, where R&D investments are a small percentage of total sales, pharmaceutical industry levels have approached 17%, which represents roughly 50% of company profit margins.

Ruffolo is quick to point out that Big Pharma, and not government agencies, funds the majority of global biomedical research. Unfortunately, the industry has been slow to tout this fact and is paying for it in the court of public opinion.

WYETH

**Ruffolo**

"The public out there does not see pharma as the innovator," explained Jan-Anders Karlsson, executive vice president of pharma research at Bayer HealthCare, "which is a missed opportunity for us and has put us on the defensive."

This then raises the question of what is happening to all of the money.

By Ruffolo's calculations, pharmaceutical R&D is witnessing an inflation rate of almost 12%, which he believes explains most of the recent increase in development costs (from roughly $800 million to $1.7 billion per drug). This means the single-digit budgetary increases most companies apply to their discovery efforts just don't go as far as they should.

BAYER HEALTHCARE

**Karlsson**

Part of the burden results from a lack of regulatory harmonization, Ruffolo suggested. He described the problem as regulatory xenophobia, complaining that U.S., European, and Japanese agencies simply refuse to work together.

"The United States will not accept comparative studies, but wants placebo trials," he explained. "Europe will not take placebos, but wants comparative studies. Thus, we have to duplicate our efforts and do both. And because they see their patient population as different from Western populations, Japan wants all tests to be performed on Japanese patients."

According to Ruffolo, although the number of Investigational New Drugs has remained steady over the last few years, the various agencies are approving fewer. Thus, Ruffolo argued, R&D cycle times at all phases are increasing, largely because of overregulation. And this is dramatically shortening the "effective" patent life of a product, where the first 10–15 years of a patent can be eaten up during development and testing.

"We are being asked to do studies that our own internal review boards wouldn't allow," he complains. "It is no longer about safety and ethics."

## The first stone

Wyeth's response to this problem has not focused exclusively on the regulatory agencies, however. Instead, Ruffolo and his team have adopted the attitude "If it's not broken, break it." Initially, they did this by pulling down barriers between various discovery and development groups within the company and linking compensation to performance across the groups. Thus, if discovery fails to reach its goals, as determined by an external review committee, clinical receives a smaller bonus. In this way, the Wyeth team has created an incentive for different groups to work together. And even at what is still an early stage, the new process is showing results.

In its new R&D productivity model, Ruffolo explained, the company tries to increase the quality of each compound in development. Thus, by involving clinical scientists earlier in the discovery process, the company looks to improve the success rate of each product. It has already seen improvements in the discovery phase with 200 fewer employees and $20 million less budget.

Wyeth is also looking to save its pipeline by moving its emphasis from life-cycle management of existing drugs to the creation of more new molecular entities. Thus, the company has set specific goals to have drugs in each phase of the discovery and development cycle and eventually to market—goals that it is well on its way to achieving and surpassing.

## Bayer-ing their souls

Similar thoughts and plans are occurring at Bayer, according to Karlsson, who said the company is looking to "re-engineer" the drug discovery process. To do this, the pharmaceutical industry will have to overcome two obstacles: productivity issues and success rates.

In the past 10 years, the pharmaceutical market has seen a strong switch from first-in-class to me-too drugs because of technical and regulatory hurdles, Karlsson

explained. However, given the current environment, he sees that process changing, and to dictate success, companies will have to move their portfolios back to uniqueness and innovation rather than rely on mass sales. Industry marketing analysts Françoise Simon and Philip Kotler recently echoed these thoughts in their book *Building Global Biobrands*.


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**Seidler**

"As clinical practice is increasingly led by evidence-based medicine, biobrands will rely more and more on evidence-based marketing—that is, a clear differential advantage established well before launch by research data and hard clinical end points," the authors write. "As regulators and payers tightly link premium prices and superior clinical performance, and as Web-enabled consumers directly access clinical data, the tendency to overbrand me-too drugs will become unsustainable, and a shift will occur from experience-based marketing to evidence-based marketing."

Key components of the changes at Bayer include a focus on core competencies, departmental integration, and active management of its product portfolio to balance risks and opportunities. For example, when Bayer managers looked at de-orphaning some of their products, they realized the required validation methods were not the company's strong point. Thus, they decided to outsource the project to other companies or academic institutions.

Similarly, company officials determined they could improve the effectiveness of their compound libraries by integrating the medicinal, combinatorial, and computational chemistry groups. Bayer also looked to harmonize its efforts in different functions and at different sites using a Web-based platform to integrate databases and analysis tools. Likewise, by developing data visualization tools, the company established grids defining each project in relation to specific criteria. This method provides stakeholders such as scientists and managers with a good overview of each project and allows them to prioritize their efforts and explain their decisions.

## Plugging pipeline holes

Perhaps most importantly, Karlsson said, Bayer also developed an internal peer-review process for its projects. The goal is to improve the success rate of preclinical to clinical transitions, which he believes will be more lucrative than simply shortening project cycle times.

But this endeavor is not without hazards. "When you have your pet project and bring it for peer review by colleagues at another site," Karlsson explained, "you have grounds for high emotion."

Nor is this approach necessarily a push for the traditional "fail cheap, fail early" paradigm. As Mark Seidler, senior engagement manager for Strategic Decisions Group, explained it, the problem with this model is that it is only good when you have more work than you can possibly accomplish; otherwise, you run the risk of prematurely terminating projects and creating gaps in your pipeline.

"If you kill projects early but have poorly predictive data," Seidler offered, "you will kill as many good candidates as bad."

He recommends that companies focus instead on improving the steps involved in getting a larger number of leads through early development. He acknowledges, however, that most companies do not have sufficient information to manage attrition rates properly.

To be successful in the future, Seidler explained, companies will have to:

- develop more rigorous and more specific backup strategies,
- evaluate therapeutics projects by targets and not by chemical entities, and
- shift emphasis to druggable targets by understanding the biology and not just counting candidate molecules.

To accomplish this, it will be important to involve top management throughout the process—not just as project hatchet men, however, but also to show support for project development.

Although each company at the conference offered its own mechanism to improve pharmaceutical R&D efficiency, they all tend to work by getting people to pull in the same direction. ■