

In the Eye of the Storm

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PHOTODISC

PHARMA IS FACING SOME TURBULENT YEARS. COMPANIES MUST PREPARE NOW TO WEATHER THE STORM.

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The pharmaceutical industry is experiencing unprecedented late-stage setbacks, product recalls, and difficulties in generating high-quality drug candidates. The problems are not specific to any one company or research effort but rather a result of the industry's limited knowledge of biology and chemistry. (See "Depth of the Problem," page 4.) Therefore, a key challenge is the industry's ability to transition to "new biology"—genomics and proteomics—which seeks to understand the causes of diseases through their biological structures and functions at the cellular level.

Those problems raise fundamental questions about the core of the industry's future:

- How can the industry accelerate the validation of new drug targets?
- How much will it cost and can companies afford to do it alone?
- Should pharma companies shift focus and resources from small-molecule drugs to biotech products?
- How much should a company invest in R&D to remain competitive?

This article explores those issues and provides bearings that will help CEOs, board members, investors, and employees navigate the stormy seas ahead.

Running Out of Targets

The pharma industry typically navigates through narrow straits defined by

- the number of validated drug targets—currently about 500, mostly receptors and enzymes
- the number of chemical entities suitable for use as pharmaceuticals: the US Pharmacopoeia lists only about 9,500

compounds that have survived safety testing through Phase I

- the economics of bringing new drugs to market.

The industry has fine tuned its growth engine to primarily develop and distribute oral dosage, small-molecule, patent-protected, blockbuster “one size fits all” drugs. That engine has generated impressive results for the last few decades, but it is beginning to sputter. (See “Productivity Gap,” page 3). One fundamental reason is that the industry has nearly exhausted the number of innovative oral drugs that can be created by combining validated drug targets with small-molecule chemicals.

Despite the excitement surrounding the Human Genome Project and other recent breakthroughs, the number of validated targets has not increased significantly. Carbohydrate-like targets or phospholipid signaling systems could yield new drug targets but are beyond R&D’s reach because of their complex chemistry. Companies are already using many of the simpler and well tolerated chemicals and are now faced with the challenge of using the remaining chemicals, which are structurally more complex, bigger, and not as well tolerated. Additionally, the increasing demands from physicians, consumers, managed care companies, and regulators have also raised the bar for new therapies.

To get out of the eye of the storm and into calmer waters, pharma companies must simultaneously improve the efficiency and effectiveness of the small-molecule R&D process, expand the scope of R&D endeavors, redistribute research expenditures, and change the organizational and financial risk-reward model to fund a broader portfolio. They must also align investor expectations with lower productivity during the next five to ten years.

New Game Plan

The industry has begun to expedite drug development and discovery through re-design and the introduction of new

technologies such as interactive voice response for clinical supply chain management, remote/electronic data capture for clinical trials management, high-throughput screening, and predictive toxicology assays. Pharma companies should continue to aggressively take advantage of new technologies, but they cannot counteract the inherent limitations of the current R&D model. On the other hand, investments in biology predictive software, combinatorial chemistry, and screening technologies have the potential to extend the use of already validated targets.

R&D labs’ management processes, particularly portfolio, resource, and outsourcing, also have room for improvement. Those areas are especially ripe for change because scientists traditionally have been reluctant to try new R&D management approaches. Pharma companies can reap significant benefits from implementing reliable project-resource portfolio management tools to better forecast demand for and supply of resources, maximize throughput, and model the risk-reward profile of R&D’s portfolio. (See “Running a Tight Ship,” *PE*, February 2002.) The information collected by those systems and the portfolio modeling capabilities will be particularly valuable as pharma companies face the transition ahead.

Because the pharmaceutical industry is more vertically integrated than others, pharma companies often perform the vast majority of activities—R&D, manufacturing, and marketing—in-house. In contrast, most large companies in other major industries focus on a limited set of high value-added activities. Auto manufacturers, for example, are primarily designers and assemblers, contracting out parts manufacturing to independent suppliers. Petroleum companies focus on exploration, development, and refining and tend not to own retail gas stations. The pharma industry can create significant value by identifying the activities that are strategically important and outsourcing those that are not. (See

Pharma’s biggest challenge is that it has traditionally not been involved with target discovery, or protein-based drugs.

“R&D Outsourcing That Works,” *PE*, March 2000.) Organizations that plan to shift their focus to biology-based R&D should take a closer look at the benefits they can gain from outsourcing many traditional discovery and development activities, such as lead optimization and clinical monitoring.

Broaden Portfolios

New biology is the future of medicine and new drug therapies. The key question is: When will it be here? Its importance is twofold: as a source of new protein-based (biotech) drugs and as a source of new drug targets based on a more specific understanding of disease pathways and determination of the optimal targets for intervention. The new biology field comprises multiple approaches and technologies.

Given the nascent nature of many technologies and their uncertainty of success, a pharma company that plans for the long haul must establish a broad-based technology portfolio. Johnson & Johnson, with its ownership of biotech units Centocor and OrthoBiotech and drug delivery specialist Alza, is the best example of a company that is pursuing such a strategy. But even J&J will need to broaden its portfolio to include a larger number of different approaches.

Big Pharma’s biggest challenge is that it has traditionally not been involved with target discovery/validation or protein-based drugs. Most biotech drugs

were discovered and developed by then start-ups such as Genentech, Amgen, and Genzyme. Those pioneers seized the opportunity by either developing protein-based therapeutics or by developing treatments for diseases caused by the disruption of a single gene.

Similarly, most drug targets were discovered and validated by academic or National Institutes of Health (NIH) researchers rather than by pharma. Drug companies, many of which have their roots in the chemical industry, took those targets and found suitable chemicals to either inhibit or amplify their activity. Today, however, the industry faces a structural problem: namely, an academic sector that is too small to validate a sufficient number of new targets to sustain the level of growth that the industry and its investors have come to expect. As a result, pharma companies are forced to take greater risks by attempting to develop drugs aimed at poorly understood, unvalidated targets.

Given their advantages in cost, convenience, and compliance, oral dosage forms have been the focus of most development efforts. But oral administra-

tion severely limits the number of chemical entities suited to become drugs. The efficient manner in which the intestines break down foreign substances means that compounds must meet a highly restrictive set of criteria, including molecule size, solubility, and polarization (Lipinski's Rule of Five). Liver toxicity is another consideration that makes many chemicals unsuitable for oral administration.

To expand the universe of small-molecule chemicals suitable for medical use, the industry must develop alternative delivery technologies, such as extended release injectibles, inhaled therapies, and drug-device combinations such as drug-coated stents. To improve administration of biotech drugs—all of which are currently injectable—the industry also needs to develop oral, viral, and liposomal drug delivery technologies for biotech products.

Collaborative R&D

Traditional pharma companies are at a disadvantage in conducting biotech R&D, discovering and validating new drug targets, and developing new delivery tech-

nologies because of their tradition, institutional bias and aversion to risk.

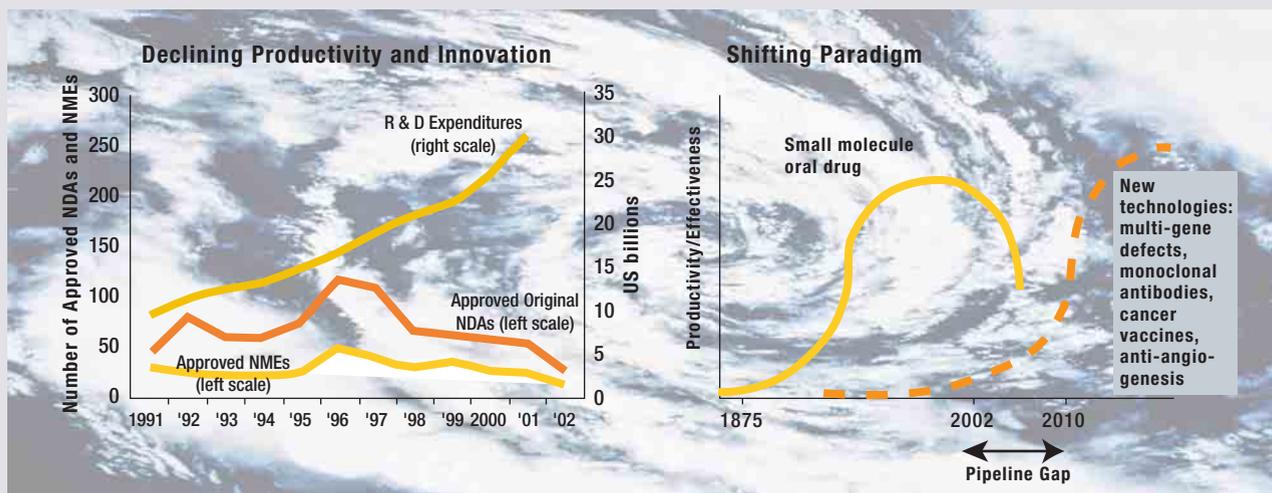
They are further hampered by a lack of skills and experience required to play in those fields. Pharma companies do not have large biology units focused on target discovery/validation or protein-based therapies. Nor do they have experience in developing and manufacturing biologic products or constructing biologics plants.

Some Big Pharma companies have acquired biotechs in an attempt to remedy that deficit, but the results have been mixed. Many of the acquired biotechs remain outposts that have neither become integrated into the mainstream R&D organizations nor have been able to exert influence on the direction of the overall R&D enterprise. Other pharmas have chosen to fund efforts by external discovery enterprises such as Millennium or Vertex Pharmaceuticals.

The significant financial investments required, the uncertain payoffs, and high—possibly, unrealistic—investor expectations have further deterred already risk-averse pharma companies from pursuing new endeavors. New ap-

PRODUCTIVITY GAP

The “new biology” is still in early development and approvals (based on current technology) are in decline, leaving pharma with a pipeline gap.



Source: Malek & Kager

PE Graphic

proaches are not always successful the first time around and frequently require repeat efforts, as is the case with monoclonal antibodies-based therapies, which have experienced serious setbacks but are now beginning to show promise. Given the need to invest in several different technologies with various risk profiles, large companies with big R&D budgets may enjoy an advantage.

The combination of those factors may be too much for a single company to overcome on its own. R&D vehicles that operate outside the confines of traditional pharma companies, but with their funding and business support, may be more successful. One such approach is the consortium model in which several companies pool their resources—human and financial—to discover and validate targets within a specific disease area or to develop new drug delivery technologies.

The SNP (single nucleotide polymorphisms) Consortium Trust is an example of a successful collaboration. Established in 1999 by ten pharma companies, leading academic medical centers, and the Wellcome Foundation, it has worked to develop and make public the map of genetic markers to enhance the understanding of disease processes. Similarly, the therapeutic area consortia would expand the knowledge of the causes of specific diseases and identify and validate new targets that the funding companies could use to develop new therapies.

Such consortia could also advance the tools used in drug discovery, be it combinatorial chemistry, screening methods, or biology predictive software. By adapting such an approach, the industry can take control of its own destiny rather than rely on the pace of academic research or

company-specific efforts—while limiting each participant’s financial risk. Those involved must first resolve governance, financing, intellectual property rights, publishing rights, and antitrust issues before the consortium model can become reality, but it can be done.

R&D partnerships focused on the development of new target or drug delivery technologies, funded by a single pharma company plus external financial investors, are another potential risk-sharing vehicle. Such partnerships would be similar to the R&D vehicles that innovative biotechs such as Genzyme have used to fund their research.

To fund those initiatives, pharma companies must rethink how they set R&D budgets. Currently, most companies either set the R&D budget as a percentage of revenues or use the R&D number as a plug in the budget. What

Depth of the Problem				
Issue	Stage	Drug	Indication	Specifics
Toxicity	Marketed drug (recalled)	Rezulin	Diabetes	Liver toxicity
Toxicity	Marketed drug (recalled)	Baycol	Cholesterol	Fatal rhabdomyolysis: muscle cell breakdown
Drug–drug interaction	Marketed drugs (recalled)	Fen-Phen	Appetite suppressant	Valvular heart disease, pulmonary hypertension caused by the combination of these two drugs, which had been approved separately
Drug–drug Interaction	Marketed drug (recalled)	Posicor	Hypertension, chronic angina	Inhibits activity of liver enzymes, leading to build-up of high levels of other drugs
Toxicity	NDA Application (withdrawn)	Vanlev	Congestive heart failure, hypertension	Agiodema: potentially fatal swelling in face and throat
Toxicity Efficacy	NDA Application (Pending in US, approved in Japan)	Iressa	Non-small lung cancer	Debilitating lung injuries, no increase in survival rate
Efficacy	Phase III (trying in other indications)	Avestin	Relapsed metastatic breast cancer	Did not meet endpoint of progression-free survival, favorable toxicology profile



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they do not do is determine R&D budgets based on a bottoms-up estimate of the resources that will be required to achieve complex, multi-year scientific objectives. To free up resources for the new consortia or R&D partnerships, pharma companies must reduce their internal R&D expenditures.

They must make hard choices about which activities to reduce or eliminate. Some companies may choose to stop small-molecule R&D altogether. Pharma companies can also free up resources by spinning off development groups focused on compounds with small revenue potential into independent, publicly traded companies. Aventis Pharma's recent divestiture of a discovery unit is yet another potential funding mechanism. Regardless of which option companies use, the transition will not be painless and will take several years.

Lowered Expectations

If returns from the small-molecule, oral drug approach are declining rapidly and the new technologies are not fully in place, then it follows logically that the pharma industry is in for a dry spell—a pipeline revenue gap. The industry must invest in the exploration and development of new fields at a time when production from existing fields is waning as a result of patent expirations and generic competition. The mergers and acquisitions taking place, such as the recent Pfizer–Pharmacia marriage, seek to address the revenue gap in the short and medium terms and “buy” time until investments in new technologies bear fruit. By and large, however, the impending revenue gap is a reality that pharma companies have yet to communicate to their constituencies. Of course, the message, when companies deliver it, should be accompanied by plans articulating the strategy, the magnitude of new investments, the risks involved, and the expected returns.

The Future of Pharma

All the data point in the same direction—the end of the traditional small-molecule, oral-formulation drug era and the emergence of therapies based on “new biology.”

The pharma company of the future will address unmet medical needs through a portfolio of approaches that include gene replacement and protein-based therapeutics in combination with various drug delivery systems. If past technology transitions are a reliable predictor of the future, the industry is about to sail into the perfect storm—one in which current incumbents face poor odds of making it safely back to port.

The greatest hindrance to pharma executives today is timidity. Computer executives who clung to their belief that PCs could never replace mainframes offer a cautionary note about the risks of ignoring emerging technologies and holding on to existing business models. Companies that will best weather the storm are those that have visionary captains at their helm who are willing to establish broad, actively managed portfolios of novel approaches and emerging technologies. They will structure new R&D vehicles—such as consortia and partnerships—to manage risks and ensure that progress is made in the shortest possible time. The next ten years will be a period of significant turbulence for the pharma industry. Those who take initiatives to fashion innovative solutions to get from “here” to “there” will emerge as the leaders. ■

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