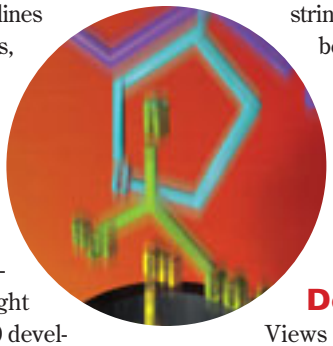
PIPELINE CHALLENGES

Major pharmaceutical and biotechnology companies take a variety of approaches to remain productive.

BY DAVID FILMORE, ANN M. THAYER, AND RANDALL C. WILLIS

Admittedly, analyzing a drug company's pipeline is more than just a numbers game. Nevertheless, like some sort of pharmaceutical industry numerology, the figures do tell a story about size and productivity. What numbers alone can't foretell, however, are the quality, value, and chances for success of drug candidates, or the strategies major drug firms are trying to fill and advance their pipelines.

In the following pages, *MDD* highlights the pipelines of the world's six leading pharmaceutical companies, based on their 2003 R&D figures, and the top two biopharmaceutical firms. Missing from the group, however, is Sanofi-Aventis, which is just emerging as the world's third-largest drug company, based on 2003 sales. It is also expected to rank about third in annual R&D expenditures, investing about $5 billion per year and having 36 compounds in clinical development. Meanwhile, the eight profiled companies—with a total of more than 700 development projects, and $30 billion in annual R&D spending and $150 billion in product sales—reinvest an average of 20% of their sales dollars in new product development.



U.S. drug industry R&D spending alone has more than doubled over the past decade, to about $35 billion, while the number of new molecular entities (NMEs) submitted for approval has dropped by nearly 50%, to about 40. This dismal return on investment comes despite an increase in the number of drugs in R&D. According to pipeline database compiler Pharmaprojects, the numbers of drugs worldwide in preclinical (4000), Phase I (750), and Phase II (1250) development have grown about 50%, 85%, and 90%, respectively, in the past 10 years.

But Phase III remains stalled, even though overall clinical development times have dropped. For the past 10 years, the number of drugs industry-wide in Phase III has plateaued at about 375 to 400. "Things look like they are going great in Phase I and Phase II, and then suddenly it goes completely wrong and just doesn't translate through to Phase III," says Ian Lloyd, Pharmaprojects' managing editor. "Part of the reason may be that companies are just not making stop-go decisions early enough."

"What they really should be doing is looking at drugs more stringently at Phase I and just say, 'Okay, we're going to boot this one now,'" Lloyd adds, which may require that companies be "more courageous in admitting they are wrong early on." In their defense, he points out that the FDA has gotten more stringent on the amount of work needed in Phase II. "But in terms of costs, you really need to clean out your closet and get rid of the rubbish as early as possible."

Down cycle or crisis?

Views are mixed as to whether the current pipeline situation represents a crisis in R&D or a short-term setback. Either way, the number of new drugs being launched is generally considered too small to sustain the major companies and meet shareholder demand for earnings growth. On top of this, many major firms are having to plug holes in their pipelines as drug patents expire and generic competition emerges.

After making tremendous gains in the 1990s, sales and earnings growth has slowed in recent years. Around the same time, expectations began escalating that new technologies—such as genomics, combinatorial chemistry, high-throughput screening, and in silico discovery—would help pick up the pace, and success rate, of R&D. However, industry observers agree that these expectations have not been met, in large part because too much was anticipated too soon.

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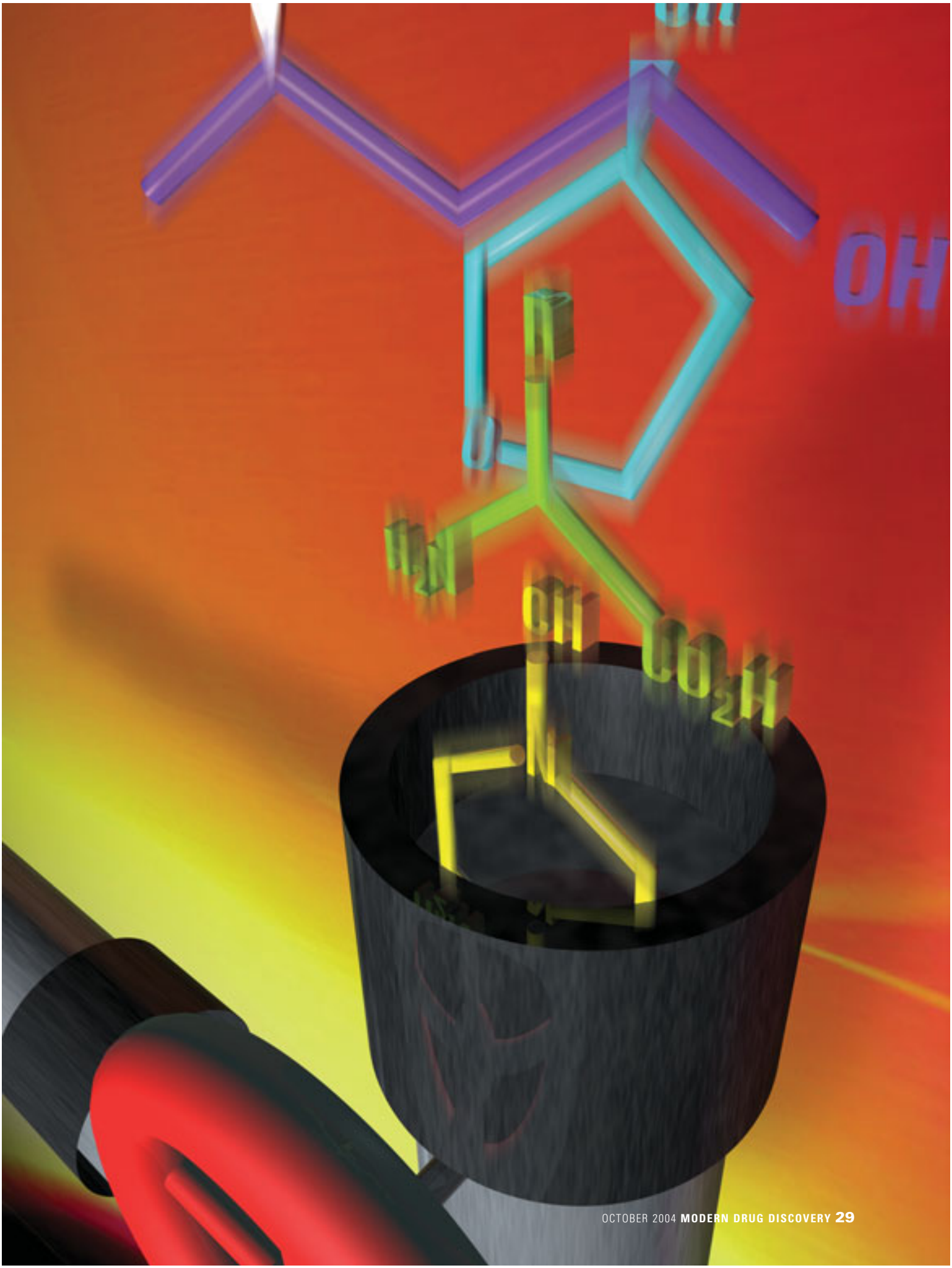

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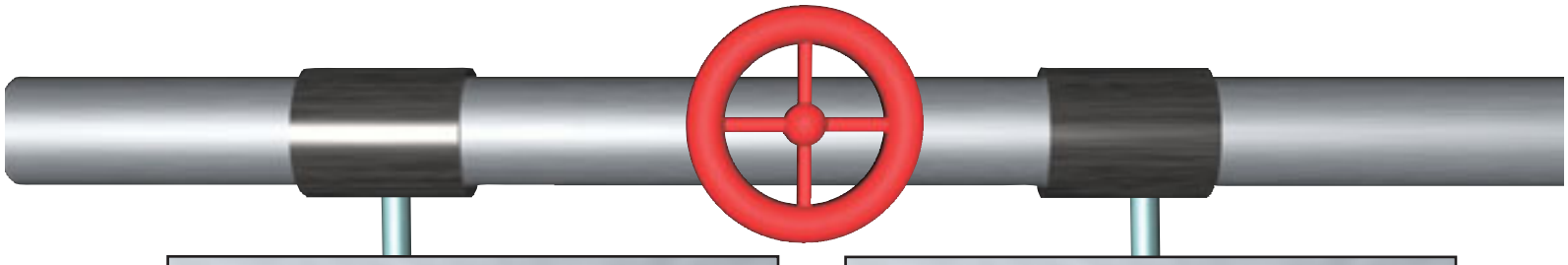


Pfizer

Pharmaceutical product sales: $39.631 billion
Total R&D investment: $7.131 billion

Pipeline

400 projects in discovery
225 development projects: 130 NMEs and 95 product extensions

Selected late-stage candidates (condition)

Lipitor/torcetrapib (atherosclerosis)
Edotecarin (topoisomerase inhibitor for cancer)
Roflumilast (chronic obstructive pulmonary disease, asthma)
Exubera (inhaled insulin system for diabetes)
Capravirine (HIV/AIDS)
Macugen (macular degeneration)
Lasofoxifene (osteoporosis)
Asenapine (schizophrenia, bipolar disorder)

Company remark

"We are on track to meet our goal of filing 20 major NDAs in the five-year period ending in 2006."

—**John LaMattina,** president, Pfizer Global Research & Development

Johnson & Johnson

Pharmaceutical product sales: $19.517 billion
Total R&D investment: $4.684 billion

Pipeline

157 late-stage drug discovery projects
154 development projects: 82 NMEs and 72 product extensions

Selected late-stage candidates (condition)

Paliperidone ER (schizophrenia)
Remicade (gastrointestinal and autoimmune diseases)
Procrit (anemia)
Levaquin (infectious disease)
Doxil (cancers)
OROS hydromorphone (chronic pain)
Reopro (cardiovascular)
Dapoxetine (premature ejaculation)

Company remark

"Molecules enter the J&J development pipeline based primarily, but not exclusively, on their degree of scientific innovation and potential ability to satisfy a high degree of unmet patient need. A careful but complete analysis which takes into account both technical (clinical, operational, regulatory) and commercial issues, is conducted before a decision is made to proceed with the development of a molecule in our pipeline."

—**Richard Bayney,** president of decision analysis and portfolio management, Johnson & Johnson Pharmaceutical R&D

"The expectations were pretty dramatic," says David Boath, partner in Accenture's health and life sciences practice. Instead of an uptick in the number of new drugs, what the industry got was a dramatic upturn in data and potential targets. "Now it's a case of sifting through that information," he adds. "Those companies that have focused on applying the technology and processes to be able to look at that data and understand it are the ones that are being successful."

Other contributors to success can include having a pipeline with some breadth that balances stages of development and high- and low-risk projects, including innovative drugs and me-toos or line extensions, Pharmaprojects' Lloyd suggests. Boath also believes that pipeline quality can be improved by rigorously assessing product candidates against financial expectations and objectives, market analysis and input, and high goals for advancing compounds.

"In terms of costs, you really need to clean out your closet and get rid of the rubbish as early as possible."

Many companies are building on their strengths in various disease areas, says Patrick Rajan, an analyst with Frost & Sullivan. For example, Novartis, Pfizer, and GlaxoSmithKline (GSK) are focusing on cancer, central nervous system disorders, and cardiovascular diseases. "The driver right now is an aging population," he explains, and producing lucrative long-term therapies for lifelong conditions.

Other companies are constructing franchises as well, Rajan notes, such as Aventis in the asthma market. Similarly, Eli Lilly had dominated the antidepressant market with its drug Prozac until generic competition emerged; just recently, the FDA approved Lilly's new drug, Cymbalta, which is expected to generate peak sales of about $2 billion. The company's pipeline has been productive, having yielded several major product launches over the past few years.

Focusing on blockbuster prospects is generally considered high risk. If they fall through, there can be gaps in the pipeline, says Kathy Smith, Ernst & Young's U.S. pharmaceutical sector leader. "If you only advance things that have a certain level of market potential, then you are going to kill a number of things that may have a greater chance," she adds. "The question would be, however, whether you can effectively manage all those products in a bunch of different disease classes, or would it really strain the organization?"

Reorganizing R&D

It's not surprising, then, that drug companies are trying a variety of approaches to manage their discovery and development pipelines. "Part of the increasing cost to get a new drug to market is the dry holes that you drill," Smith explains. "Is just more dollars spent better, or are some companies better able to strategically place their bets?"

"Having more dollars allows companies to diversify their bets so they can try a number of technologies and the like," she continues. "But you are seeing companies take a variety of approaches [to better place their bets], whether it's consciously diversifying, and trying to decentralize and get closer to the science and some of the innovations, as opposed to a more traditional big centralized R&D effort."

Some companies have assembled sizable R&D operations and larger pipelines through mergers and acquisitions, as may soon be the case with Sanofi-Aventis. Pfizer, with its recent acquisitions of Warner-Lambert and Pharmacia, dominates the industry with an estimated $7.9 billion in 2004 R&D spending and hundreds of research projects across 18 therapeutic areas. On the other hand, GSK has been criticized for getting only a handful of new drugs approved since its merger with SmithKline Beecham in 2000. Still, it runs second behind Pfizer in NMEs in development.

Consultants say it's unclear whether consolidation breeds success. "You end up with such a huge, increasingly large organization, and the products it takes to sustain even high single-digit growth become quite substantial," Smith says. "Certainly in the short term, mergers do bolster pipelines, but I think the answers are still very mixed as to whether, at the end of the day, these present long-term results."

GSK, Wyeth, Roche, and Novartis are among companies that have been organizing their R&D operations to increase productivity,

GlaxoSmithKline

Pharmaceutical product sales: $29.0 billion
Total R&D investment: $4.577 billion
Pharmaceutical R&D investment: $4.441 billion

Pipeline

53 preclinical candidates
148 clinical development projects: 83 NMEs, 20 vaccines, and 45 product extensions

Selected Phase II and III candidates (condition)

480848 (atherosclerosis)
Etaquine (malaria prophylaxis)
Talnetant (irritable bowel syndrome)
572016 (solid tumors)
Nelarabine (acute lymphoblastic leukemia and lymphomas)
353162 (antidepressant)
274150 (asthma, chronic obstructive pulmonary disease, allergic rhinitis)
Cervarix (human papillomavirus vaccine)

Company remark

"GSK's R&D is structured to take advantage of size at the beginning and the end of the R&D process where large-scale research is needed—such as screening targets against compounds and conducting large-scale clinical trials. However, to bridge the interface between discovery and development, the organization is divided into new, small, biotech-like business units—Centers of Excellence for Drug Discovery (CEDD)—that can take full advantage of flexibility and focus."

—GlaxoSmithKline statement

Novartis

Pharmaceutical product sales: $16.020 billion
Total R&D investment: $3.608 billion
Pharmaceutical R&D investment: $3.079 billion

Pipeline

47 advanced preclinical candidates
78 clinical development projects: 53 NMEs and 25 product extensions

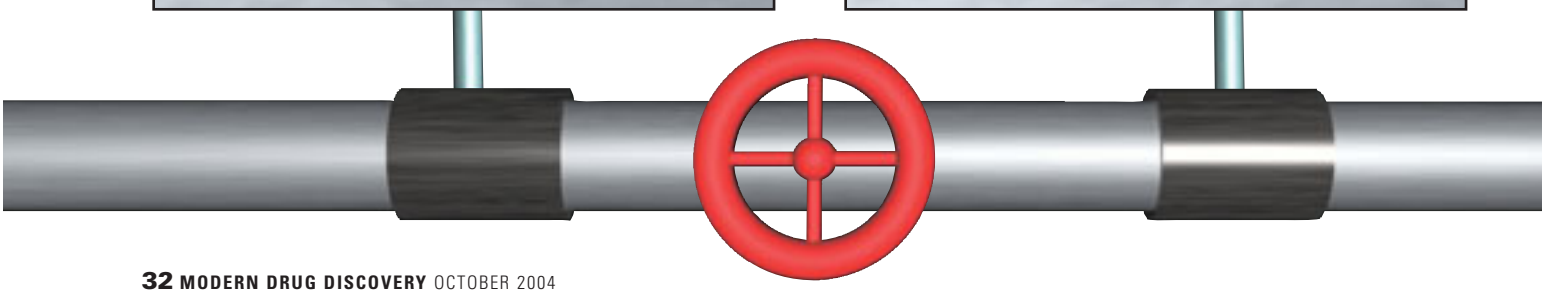
Selected late-stage candidates (condition)

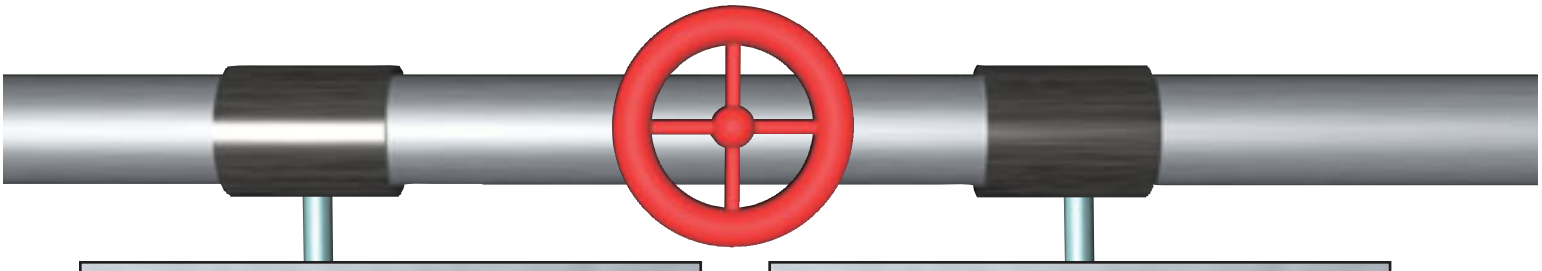
TCH346 (Parkinson's disease and amyotrophic lateral sclerosis)
LAF237 (Type 2 diabetes)
PTK787 (solid tumors)
FTY720 (immune modulation)
ASM981 (inflammatory skin diseases)
SMC021 (osteoporosis)
LDT600 (hepatitis B)
PR335 (myopia)

Company remark

"Pharmaceuticals remains an attractive market for top innovators, and we will leverage our commercial successes and strengths to increase the number of blockbuster products in our portfolio."

—**Daniel Vasella,** chairman and CEO, Novartis AG





AstraZeneca

Product sales: $18.849 billion
Total R&D investment: $3.451 billion

Pipeline

77 preclinical and clinical development projects: 52 NMEs and 25 product extensions

Selected late-stage candidates (condition)

AZD0837 (thrombosis)
AZD0865 (acid-related gastro-intestinal diseases)
Merrem (soft-tissue infections)
ZD0947 (overactive bladder)
AZD3409 (solid tumors)
AZD8309 (rheumatoid arthritis)

Company remark

AstraZeneca's "approach is therapy-area-led, with scientific, medical, technical, and ethical input and control being provided by large, multiskilled discovery and development organizations. This offers a number of advantages, including sharing of best practice in terms of science and technology, and efficient use of resources across a multisite, global organization."
—AstraZeneca 2003 Annual Report

Roche

Pharmaceutical product sales: $16.97 billion
Total R&D Investment: $3.75 billion
Pharmaceutical R&D investment: $3.11 billion

Pipeline

62 preclinical and clinical development projects: 52 NMEs and 10 product extensions

Selected late-stage candidates (condition)

R744 (cancer-related anemia)
R873 (male erectile dysfunction)
R1558 (bacterial infection)
R1628 (rheumatoid arthritis)
R1496 (obesity)
R1497 (Parkinson's disease)
R1454 (solid tumors)
R411 (asthma)

Company remark

"With our well-balanced portfolio of clinically differentiated medicines, the Roche Group is well positioned to meet future health care challenges and ensure the company's ability to achieve significant growth in the years ahead."
—**William M. Burns,** head of Roche's pharmaceuticals division

streamline operations, and possibly cut costs. Many are trying to overcome the bureaucracy of large organizations to improve information flow and decision-making while still maintaining critical mass for R&D.

GSK has created seven entrepreneurial research areas with therapeutic focuses. As a result, the company has substantially increased its late-stage pipeline, including NMEs, and anticipates a record number of filings between 2004 and 2008. Likewise, Novartis, which has R&D operations in strategically chosen diseases areas, has upped its number of clinical trial projects since 2000. It also reports that it has led the industry in NMEs approved—with 11—between 2000 and 2003.

Wyeth recently began using cross-functional business teams within its discovery organization to help define strategy, handle budgets and resources, and optimize pipeline value while managing risk. Its new approach also links scientists' performance and compensation. As a result, over the past 3 years the company has moved 12 novel compounds per year into development, compared with an average of just 3 per year in the 1990s.

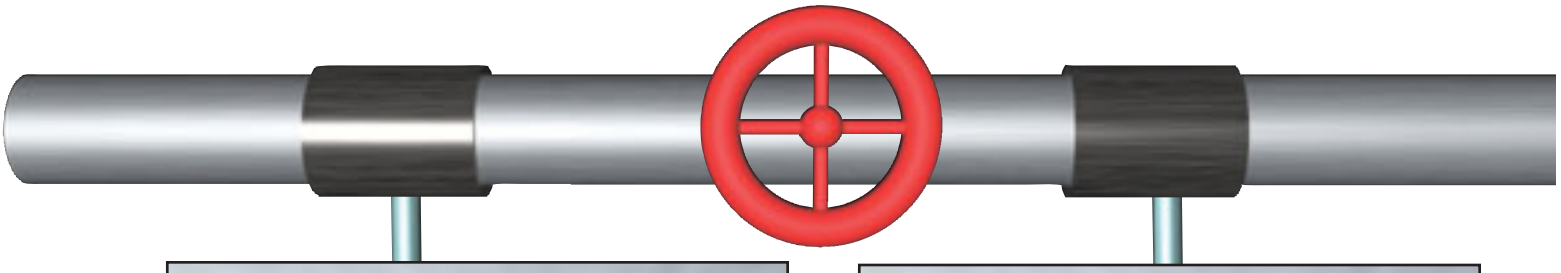
The idea behind such changes is "about getting all of the scientists really focused on trying to achieve the strategy of the organization," Boath explains. "I've seen companies make the biggest leaps when they start looking at the drug discovery area as a business. It's about cascading goals and objectives down through the layers of management to actually reach the scientists at the bench so they understand what it is they should be doing."

"Science has to be able to produce something that's going to be of value," he continues, emphasizing the need for management discipline and metrics for better decision-making. "I think you are seeing a behavioral change in a lot of scientists, and the ability of senior management to drive discovery organizations and really focus on value and output. And I think its increasing productivity and innovation."

"Those companies that have focused on applying the technology and processes to be able to look at that data and understand it are the ones that are being successful."

Innovation engine

Despite the new approaches, new technologies, and a wealth of new information, drug R&D is still challenged by understanding exactly how drugs will work and why they may fail. Target validation remains a bottleneck as well. Thus, the hurdle of getting past Phase III trials and launching more NMEs continues. To find innovative technologies and therapeutic



Genentech

Product sales: $2.621 billion
R&D investment: $0.722 billion

Pipeline

33 preclinical and clinical development projects: 9 NMEs and 24 product extensions

Selected late-stage candidates (condition)

Avastin (pancreatic, colorectal, breast, lung, and renal cell cancers)
Lucentis (macular degeneration)
Rituxan (non-Hodgkins lymphoma, lymphocytic leukemia, vasculitis, nephritis, lupus, and rheumatoid arthritis)
Veletri (acute heart failure)
Omnitarg (breast, lung, and ovarian cancers)

Company remark

"At Genentech, we are rewriting the medical textbooks with our first-in-class therapies. We are focused on sustaining innovation, creativity, productivity, and momentum in our pipeline to move us towards our product development goals for Horizon 2010."

—**Susan Desmond-Hellmann,** president for product development

Amgen

Product sales: $7.868 billion
R&D investment: $1.655 billion

Pipeline

19 clinical development projects: 18 NMEs and 1 product extension

Selected late-stage candidates (condition)

AMG531 (idiopathic thrombocytopenia)
AMG162 (osteoporosis)
GDNF (Parkinson's disease)
AMG162 (metastatic bone disease)
AMG714 (rheumatoid arthritis)

Company remark

"To be successful, the commercialization process has to be a deeply collaborative one from the outset. Together, we ask the questions: Is there a need in the marketplace? What unique benefits might the product offer? Can we advance the practice of medicine? Amgen is not interested in developing 'me-too' therapies or treating diseases for which a number of effective treatments already exist."

—**George Morrow,** vice president of global commercial operations

approaches, many large companies have turned to smaller drug discovery firms.

The biotech industry is generally viewed as the leading source for innovative drug products. New biological drug approvals have been climbing for the past 10 years and have been making up an increasingly larger portion of all drugs approved in recent years. About 1800 biotech drugs are in development, with about 340 in late-stage testing or awaiting approval.

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To tap into these, major drug firms are licensing products and setting up development partnerships, often to jump-start or fill holes in their pipelines. Merck, for one, has accelerated its partnering activities in the past few years to rebuild its pipeline, while others, such as Johnson & Johnson, have made numerous biotech acquisitions. For Roche, a 58% ownership stake and connection with Genentech since 1990 have contributed in a big way to its earnings.

Pharmaprojects reports that 24% of drugs in active R&D are available for licensing, while another 25% are already licensed out or in co-development. There's also a pool of drugs out there that could be, but are not, being developed, Lloyd says, having been dropped for "strategic" reasons, such as a shift of corporate focus or resources, rather than a lack of efficacy or adverse events.

But while the biotech industry spawns success, it is also maturing and facing new risks, including longer clinical development times and the need for financing. And, after years of leading with innovative products, biopharmaceutical producers may soon find themselves on the defensive. Amgen and Genentech, which together account for about a third of the biotech industry's top drugs, could soon face generic competition when patents expire.

"An interesting issue that companies may have to deal with over the next several years is whether there is going to be more emphasis on cost effectiveness or value added to a new drug," Smith says. "Are drugs that are really innovative or meeting a new unmet need going to have the advantage over just the follow-on products? I think a lot of companies are exploring that and trying to understand how much emphasis is going to be put on that as new drugs go through the FDA and then look for reimbursement approval." ■