Employment Opportunities

for 2004 and beyond

BIRTH OF A DRUG

PHOTO: ROCHE

For chemists, there's many a role to play in the long process of drug development.

BY AALOK MEHTA

IT'S A FAMILIAR TALE TO CHEMISTS: years of rigorous testing before making the transition from theoretical inquiry to practical application, a big run-up in expenses, and a demanding final defense before entering the real world to make money.

It's the story of a drug.

Modern drug discovery has become an increasingly time-consuming and expensive process. A long laboratory research and development phase is followed by extensive testing in clinical trials; then the FDA painstakingly reviews the results before a drug candidate can win final approval. In the end, the development of a single drug can leave behind more than 15 years of work, thousands of dead-end research leads, and hundreds of millions of dollars in associated costs.

Still, drug discovery is a remarkably robust field. The pharmaceutical industry continues to weather tough economic times better than most other sectors and continues to pour money into R&D. New treatments are constantly emerging, giving hope to both the terminally stricken and the perpetually pained. And for chemists, drug discovery offers numerous jobs with a very real purpose and a human face.

"We're clearly in this business to make an impact on the devastating diseases that affect our country and the whole world, really," says John W. Benbow, a senior principal scientist in the discovery division of Pfizer Global Research & Development, Groton, CT. "I know people who are personally affected by the diseases I work on—I have a personal stake in this. The big reward is to bring a compound to market and hear from people, hear that you made a difference in their lives."

But for chemists working in drug discovery, such an outcome is rare. The bulk of their work is spent on compounds of a much more humble nature—the chaff that is inevitably tried, tested, and discarded in the search for suitable clinical candidates.

Generally, drug discovery efforts are organized by therapeutic targets. A particular disorder is often the sole objective guiding multidisciplinary teams of discovery researchers

"Chemists are actually involved in all aspects of the drug discovery process, from the inception of the idea to the handoff of a potential chemical candidate to the development organization," Benbow says. "And it's very interdisciplinary; we bring all the forces to bear on the projects we're doing. Everyone is encouraged to contribute and drive progress forward." Biologists, biochemists, medicinal

PHOTOS: NOVARTIS/ROCHE

chemists, physical chemists, computational chemists, organic chemists, and synthetic chemists all have their roles in the process.

Biochemists and molecular biologists usually initiate the process by conducting high-throughput screenings of compound libraries, looking for molecules that show the desired reactivity. They design and conduct "the wonderful assays that generate so much excitement at pharmaceutical companies," says Edwin Villhauer, a Novartis discovery medicinal chemist who recently moved to process development at Novartis's East Hanover, NJ, site. "There's been quite a dramatic increase here in the amount of data that these assays can generate."

Medicinal chemists, usually with a synthetic or organic chemistry background, analyze the assay results, looking for promising compounds. They then tweak these leads—focusing on potency, selectivity, solubility, bioavailability, and metabolic stability—to create a compound that delivers itself to the appropriate target with low toxicity and few side effects.

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Medicinal chemists are vital to drug discovery, but they're not easy to find. "Good-quality medicinal chemists start off as synthetic organic chemists and learn medicinal chemistry on the job," Villhauer says. "It takes several years for them to get the appropriate background. Not many schools currently teach what we do."

The discovery process also harnesses the power of other specialties. Cheminformatics experts are being used increasingly to sort and manage the enormous amounts of data generated by drug discovery groups. They coordinate with physical chemists, who are tapped for their ability to generate crystal structures, and with bioinformaticists, who can create models for testing drug behavior even in the absence of other structural information. In later stages, biologists conduct animal testing of promising candidates.

"It's a job that's highly rewarding," Benbow says. "There are always challenges—puzzles to solve—that are intriguing to us as scientists. We deal with a lot of chemical structures and employ our skill at getting around tough problems. Our expertise is always being tapped."

Still, the attrition rate of drug candidates and the open-ended nature of discovery goals "can be frustrating. It's hard. I wish it didn't have to be so difficult sometimes," he says. It's also long: Discovery can take up to a decade and usually averages around seven years.

The process development stage, which starts about six months to a year before the first application is submitted to FDA, in contrast, involves mostly well-defined challenges and objectives. Development chemists, who usually have organic chemistry backgrounds, work on scaling up the synthesis and manufacture of strong drug candidates, which are often needed in large quantities during the clinical trial period. They often continue to refine these processes until well into the second stage of clinical trials.

Development chemists also work with chemical engineers on setting up true bulk manufacturing processes. "You collaborate quite tightly with chemical engineers—they take your process that worked on the 500-g scale and take it to the hundreds-of-kilograms scale," Villhauer says. Development chemists are also sometimes called on to help when such scale-ups create unexpected problems, like an as-yet-unseen crystal form.

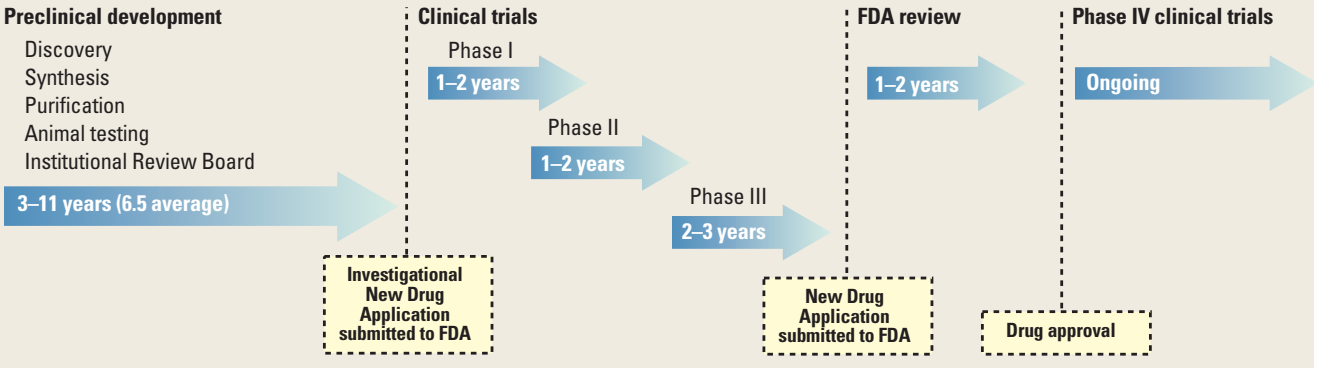
"A colleague once said to me, 'There'll never be a bottleneck from the process chemistry team in drug development. Process research comprises the best chemists in the industry, and we will get the job done in time,'" Villhauer says. "We work long hours, but we meet our goals. If you love organic chemistry, process is the way to go."

With animal testing results and a small-scale manufacturing process in hand, the drug candidate now faces the first of several important FDA checkpoints. The company gathers all of the R&D results and completes a proposal for testing the drug candidate in humans, including information on what populations will be tested and what doses and drugs will be administered, along with a set of goals and a preliminary schedule. The FDA reviews the package, known as an Investigational New Drug Application (INDA), and decides whether the drug can enter clinical trials.

SOURCE: FOOD & DRUG ADMINISTRATION

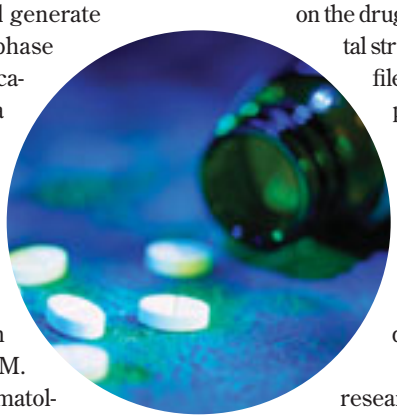
GROWING PAINS

Moving a drug from concept to finished product can take more than a decade



At this stage, too, the company runs its clinical testing proposals past an Institutional Review Board. An IRB—whose approval is needed before any clinical testing can begin in the U.S.—is an independent committee of physicians, statisticians, researchers, and nonscientists who ensure that medical institutions conduct biomedical trials ethically and protect the rights of the participants. Through periodic reviews, they make sure participants are informed of the risks and that adequate safety measures have been set up by the testers.

Assuming approval of the INDA, clinical trials are scheduled. Clinical testing has three main phases. Phase I trials are conducted on a few people (20 to 80), usually healthy volunteers, to evaluate a drug's safety, identify side effects, and determine appropriate dosages. In Phase II, a larger group of patients (100 to 300) is tested to further evaluate safety and generate preliminary data on effectiveness. The third phase consists of 1000 to 3000 patients from many locations, and it confirms effectiveness, creates a side-effect profile, and compares the drug's effects to other treatments.



The clinical testing stage is a major transition in the drug development process. For the first time, patients are directly involved, and a new set of experts goes to work: doctors. Clinical scientists "have an M.D. degree as a rule," though sometimes they also have a Ph.D., says Richard M. Goldberg, professor and division chief of hematology/oncology at the University of North Carolina School of Medicine, Chapel Hill. As associate director of clinical research for UNC's Lineberger Comprehensive Cancer Center, Goldberg has conducted all three stages of clinical testing on a variety of cancer treatments.

Many drug trials are initiated by pharmaceutical companies, which often recruit doctors at national meetings to conduct the trials. "There are major hurdles to overcome when starting clinical trials," Goldberg explains. For example, doctors need to secure approval from both the pharmaceutical company and the institution at which the trials will be conducted, as well as work in committee to finalize the design of the trials. After those hurdles, the actual work can begin: providing periodic treatments, monitoring patients, recording side effects, adjusting doses, and noting activity and toxicity in comparison with standard treatments. The researchers also review drug applications to the FDA, answer FDA queries, and consult statisticians to assess their data.

"The biggest benefit to randomized Phase III testing, which compares new drugs or drug combinations, is that it allows us to practice evidence-based medicine," Goldberg says. "On the basis of these trials, we know where to use drugs and how to use them. For example, until 10 years ago, there was just one drug to treat colorectal cancer; now we have five new drugs to use—two in the past few months. We can offer a lot more to patients than even a few months ago." But like discovery work, clinical testing can be frustrating. Only about one in five drugs that enter clinical testing is eventually approved for sale by the FDA. Most of these are eliminated after Phase I trials.

After Phase III, the biggest challenge of all is on the horizon: a New Drug Application to the FDA. The NDA, which is a summary and analysis of all the data accumulated on the drug so far, is the final test before the drug is approved for the market.

"Our review really requires an interdisciplinary group of scientists," says Moheb M. Nasr, director of the Office of New Drug Chemistry at the FDA's Center for Drug Evaluation & Research. Process, organic, analytical, physical, inorganic, and medicinal chemists; chemical engineers; biochemists; industrial pharmacists; pharmacologists; statisticians; and clinical scientists are all involved. "We assemble teams of interdisciplinary scientists," Nasr adds, "creating a high level of expertise in a lot of very sophisticated areas."

During the review process, which can take up to two-and-a-half years (less for priority drugs), the FDA reviews all the information on the drug, checking over discovery, scale-up, stability, crystal structures, levels of impurities, and toxicological profiles, with special emphasis on the manufacturing process. "We believe the process is the product," Nasr says. "The product is fully understood when it can be manufactured consistently and high in quality." As part of its efforts, the FDA encourages frequent meetings with drug companies both prior to the application—to ensure that all the relevant information is included—and during the approval process.

Chemists and related scientists also conduct research at the FDA's labs, working on analytical methods, formulation science, and instrumentation to assist in drug approval efforts. "The FDA and industry have a common goal: a quality product available to the public in a reasonable amount of time and at the most reasonable cost," Nasr says.

Like other jobs, work at the FDA has its ups and downs. "The work environment is excellent," Nasr says. "We provide a service to the public, we make an impact on approval, and our work can benefit millions of people." Scientists also have a unique opportunity to influence policy development at the organization. But the workload is heavy, pay is generally inferior to industry, and scientists are expected to keep on top of developments in many fields.

If everything passes muster, the FDA will approve the candidate for sale. The product has beaten the odds, completing its odyssey from compound library to store shelf. Only then will the heavy investment in money and workforce finally pay off.

After approval, companies can continue to collect information on how their drug acts and its long-term side-effect and stability profile, and they can test the drug for new applications. This optional stage is known as Phase IV trials.

Many scientists have a hand in the long journey to drug approval, and though approval is pretty rare, when it does happen, it's a feeling like no other. "To touch the human race—to actually make a difference—that's a great feeling," Pfizer's Benbow says. "That's what working at a pharmaceutical company means."

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