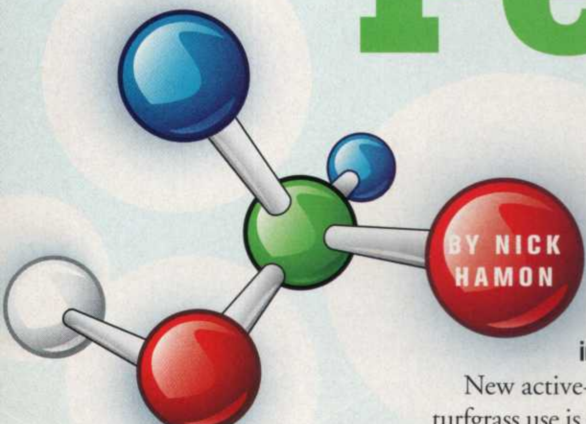
Pedigree of a Pesticide



It takes a lot of time, money, research and testing to bring a new active ingredient to market

BY NICK HAMON

Most golf course superintendents probably don't think much about the science and technology behind the products they choose to keep their turf free of weeds, insect pests and diseases.

New active-ingredient development for turfgrass use is not so dissimilar from that of a new pharmaceutical: Costs are high; it takes many years to get to market, and the chances of success are not guaranteed, even in the final stages of development. In fact, one might argue that pesticide development can be more complex than drug development because it includes not only efficacy and human safety testing but also detailed and costly monitoring of the environmental fate of the product.

Some facts and figures may help to put the process in perspective: Many companies spend more than $650 million annually on research and development. R&D involves not only the discovery of new active ingredients but also the continued support of existing products. In a study carried out by Phillips McDougall for American Crop Life and the European Crop Protection Association, the estimated cost of bringing a new agrochemical to market in 2000 was about $200 million.

Today, the costs are considered to be closer to $240 million. As well as in-house R&D, Bayer Environmental Science alone invests about $3 million annually with about 42 major universities in North America. Their work varies from basic research on the mode of action of new chemistry to efficacy profiling on pests, weeds and diseases.

It takes eight to 10 years on average to get a new active ingredient from the laboratory bench to the customer. And if you invest $250 million in new technology, you clearly do your best to protect your investment with patents. The life of a patent in North America varies from 17 to 20 years, which means a company has only about 10 years after launch to recoup its investment before generic companies can encroach.

How are new active ingredients discovered? Every year, our company runs as many as 1 million new molecules through a complex biological screening process. Much of the work is done with a process called combinatorial chemistry, in which new molecular structures are synthesized using complex robotics. Robots are also used to measure and weigh these chemicals, testing them for biological activity in biochemical screens. These biochemical screens are often cell-based systems involving ion channels, receptor sites and signaling pathways. We are constantly researching new modes of action to improve performance, reduce costs, improve the toxicological and ecological profiles and combat resistance to established classes of chemistry.

Despite more than half a century of industry research, the number of different modes of action available is surprisingly small. Using insecticides as an example, the most commonly used active ingredients still offer only three distinct modes of action:

- acetylcholinesterase inhibitors (organophosphates and carbamates);
- sodium channel modulators (synthetic pyrethroids); and

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• nicotinic acetylcholine receptor agonists and antagonists (imidacloprid).

Some of the chemistry under research involves well-understood modes of action, but much of the effort goes into the search for biologically active compounds among unknown chemistries. These biological screens run on nanograms or micrograms of active ingredient, and few (less than 1 percent) show biological activity on cellular systems or on whole organisms.

Compounds that do elicit biological responses will progress to further levels of screening, eventually encountering many target and non-target organisms, such as weeds, fungi, nematodes, mites or insects. It is at this point that chemists will work closely on redesigning the structure of the new active molecule to optimize toxicology, biological performance, costs, physical properties and environmental fate.

Of the million compounds our company tests annually, fewer than 20,000 make it through the initial screens, and perhaps only 750 will show promising activity in further studies. All of these compounds will get full biological and chemical profiling in laboratory and glasshouse trials, but fewer than 10 per year will end up being field tested at one or more of the 25 research farms that the company manages around the world.

Because the target pests, methods of application and technology needs of the turf and pest control markets are different than agriculture, Bayer Environmental Science has its own Development and Training Center in Clayton, N.C. At the Clayton site, scientists test new products on more than 40 cultivars of turf and as many as 30 different insects and diseases important to golf course superintendents. From the synthesis of a new molecule, it often takes three to four years before any field testing is done. After several years of field screening as well as intense research on manufacturing process, formulation, mammalian toxicology, environmental fate and mode of action, the company will make a decision on whether to promote this new compound into full-scale development.

Full-scale development means a further investment of many millions of dollars, with no guarantee that the new chemistry can jump

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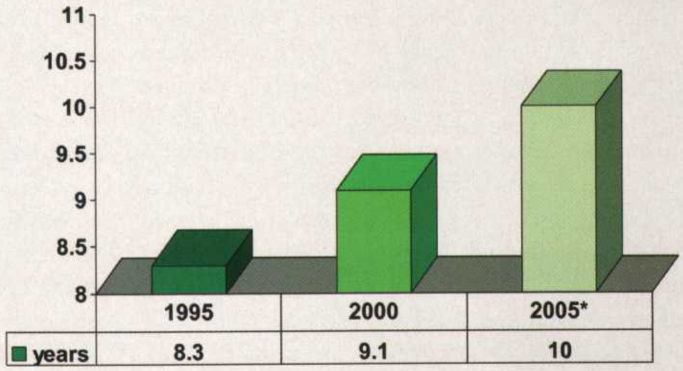
Time from Discovery to Market

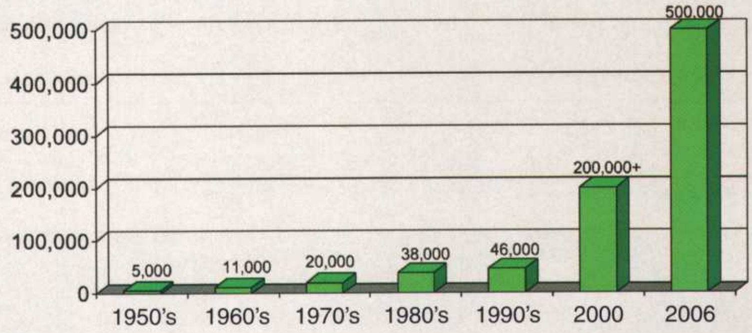
Number of years between discovery and first significant sales



Phillips McDougall for American Crop Life/European Crop Protection Association

* Bayer estimate

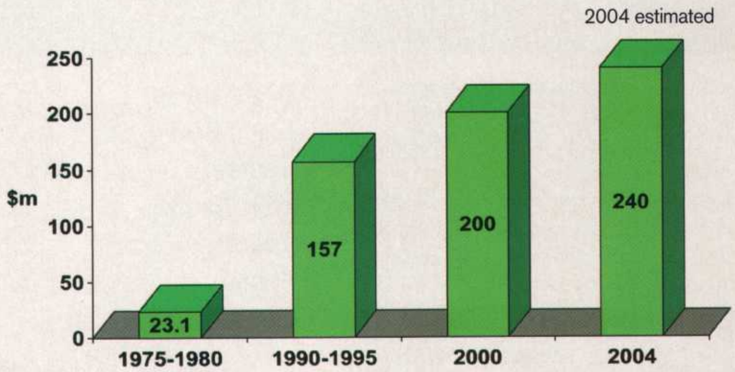
The number of compounds Bayer CropScience screens per year to discover one or two new commercial products



Cost of Developing a New Pesticide

Phillips McDougall for American Crop Life/European Crop Protection Association

(Aventis, BASF, Uniroyal, Dow, DuPont, FMC, Monsanto, Sumitomo, Syngenta)



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all the cost, regulatory and efficacy hurdles that it will face in the next four to six years of the development process. Making a decision to invest in a new active ingredient is not all based exclusively on biological performance. Every detail is scrutinized: how large the market might be, what the competitive products are, whether the product is a good strategic fit, whether Bayer will recoup its $240-million investment over the life of the product and what risks are associated with making a "go" decision.

Once in full development, a whole new team of scientists will shepherd the product through a complex package of new tests. To get an EPA or EU registration, more than 150 regulatory studies will be done during a four-year period, including product chemistry, ecological toxicity, mammalian toxicity, nontarget plant and insect toxicity, environmental fate, metabolism and residue chemistry and risk assessment. Work will commence on:

- chemical synthesis and production (scaling up from a few pounds to making hundreds of tons);
- manufacturing (do we need to invest $50 million on a new manufacturing plant or can we adapt an existing plant?);
- how best to formulate and deliver to the target organism; and
- optimizing bioavailability (drop size, retention, rainfastness, systemicity, crystal size of dry deposit on surface).

Thousands of field trials will be carried out on farms around the world. At the same time, we will work closely with university experts to get their input on performance and benefits compared to existing products. If all goes well — after eight to 10 years from the initial synthesis and discovery, an investment exceeding $200 million, and the involvement of thousands of scientists and university researchers — the new product will be granted a label of registration.

As exciting as it is to get a new product to market, the work of the scientist has only just begun. Thousands of trials will be monitored closely to better understand performance and mode of action. Formulations will be optimized continuously for new pest targets. Also, compatibility studies, benefits of mixtures, application timing and techniques will be analyzed for many years.

In fact, some of the most intensive research goes into the continuous improvements of existing products. At any one time, we might be looking closely at up to six new active ingredients per year. Many will not make the transition into the environmental science markets, but a few will have the perfect profile for use by professionals in turf, ornamental or urban pest management. ■

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