Why It Takes 10 Years to Bring Products to Market

By Joe Yoder

To score a home run in baseball, the runner has to touch all four bases. Companies developing plant products for the Green Industry have dozens of bases to touch before even getting to first base. If that sounds confusing, be assured that it is.

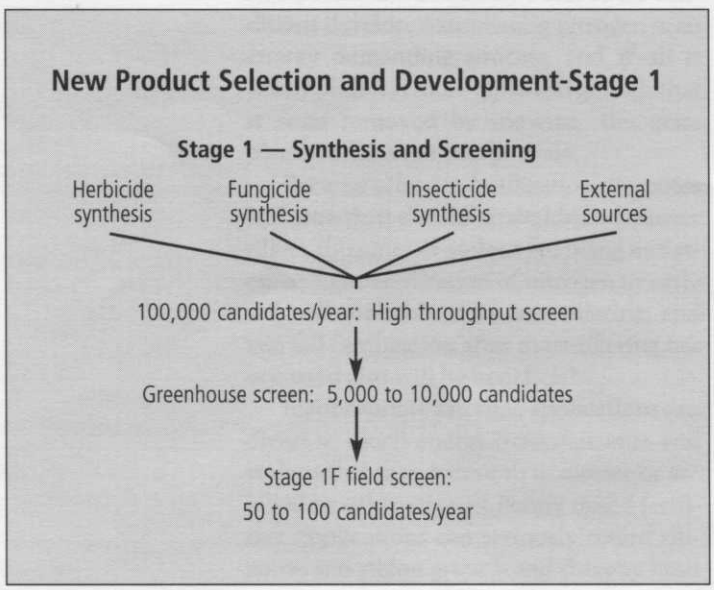
Five years ago, large basic manufacturing companies screened between 5,000 and 15,000 compounds a year. Today, it's between 50,000 and 100,000 per year.

Even to an insider, the complexities of bringing a new herbicide, fungicide or other pesticide to the market are bewildering. While the starting point is always grower needs, there are a host of other factors that go into developing a product.

The United States Environmental Protection Agency's (EPA) policies, requirements of research and the competitive sales environment established by other manufacturers all play a role in the game. It is a process of asking questions, looking for answers and taking risks on unknowns:

* What will the end user need or want?
* Will the material be safe?
* What does the EPA want to register?
* What will the competitors have brought to market?

Just to add a degree of difficulty, those questions all have to be answered in the framework of what the "right" answers to those questions will be in 10 years. That's because it will take 10 years to bring a just-discovered molecule to the market—if all goes well.



Basic compounds

For most basic manufacturers, the compound discovery process begins with the synthesis and screening of molecules. Usually, newly synthesized molecules arise from one of three sources:

l. Bio-rational in origin – that is, they are made to target a known site of activity in the plant or pest.

2. An area of known chemistry with known activity – that is, there is a lead compound, either from previous development work or found in nature; and the chemist is working around this lead looking for superior activity not already covered by a patient.

3. A novel compound with no known connection to the desired activity. Many compounds in this last group are accessed from nonagricultural chemical groups and can be the source for "new to the world" products.

These molecules are then sent through a screening process using complex laboratory and greenhouse tests.

As recently as five to 10 years ago, more large basic manufacturing companies screened between 5,000 and 15,000 compounds a year. As a result, the screening process was a bottleneck.

Today, these larger companies are screening 50,000 to more than 100,000 compounds per year, thanks to the great strides that have been made in miniaturizing, automating and refining the screening process.

Many companies have made arrangements to access catalogues of molecules from all over the globe, originally synthesized for a diversity of reasons. It is not uncommon for more than 50 percent of the screened molecules to come from such sources.

Of the 100,000 compounds screened in the labs, only 5,000 to 10,000 will go on to more complex and space intensive greenhouse screening. Of these, only about 50 to 100 will go to initial screening in the field, usually on experimental farms.

For a material to get past the screening process and make it to first base, there still are questions that must be answered. Researchers investigate the primary characteristic that is being sought. They ask: does the molecule do anything that is biologically interesting? Is it active? If these questions are positive, a company will begin to intensively research its molecule efficacy and crop safety.

Efficacy and crop safety are the first items to be addressed in the field. To do this, the surviving candidate compounds are taken out of the lab and greenhouse and used under conditions that approach field conditions. Often, this will be a worldwide testing program conducted at research farms specializing in this type of testing.

In addition to efficacy confirmation and crop safety, the goals in the initial field trails are analogue separation, rate definition, formulation type definition and leads for future synthesis.

Testing in stages

Up to this point, all work has been conducted in what is often referred to as Stage 1. After initial field results have been analyzed, the top one or two leading candidates may be promoted into Stage 2, if deemed worthy of further investment.

During Stage 2, the knowledge base will be expanded by conducting additional field testing and preliminary environmental fate, toxicology and process development studies.

It is during Stage 2 that "red flags" or issues can come up from a variety of sources including efficacy or crop safety problems, toxicology or environmental concerns, patent assessments, production cost estimates and market potential. Failure to clear any of these hurdles will result in a material being eliminated from play.

Assuming the answers to the questions in Stage 2 are promising, then a decision to promote to Stage 3 or full development will be made.

Now it is time for a potential product to put on its game face and get serious. Up

New Product Development — Stage 2

Stage 2 — Continued field and preliminary safety screening: 1 to 3 candidates

Safety screening (short-term lab studies)

- Toxicology — Oncogenic potential (Ames, SAR)
  - Teratogenicity (In vitro, In vivo)
- Environmental Fate — Environmental load (rates/intervals)
  - Persistence (pilot soil metabolism)
  - Mobility (KoM, Rmf)
  - Bioaccumulation (Log P)
- Ecological Effects — Aquatic toxicity (fish, Daphnia LD_{50})
  - Avian toxicity (oral LD_{50})

Major Study Areas — Stage 3

- Mammalian toxicology
  - 90-day sub-chronic studies
  - Chronic studies — 2 years for rats; 18 months for mice
  - Other studies — reproductive and neurotoxicity
- Metabolism — rat, mouse and crop
- Environmental metabolism and fate — soil and water
- Residues

* Ecotoxicity

- Acutes in fish, birds and invertebrates
- Avian reproduction
- Fish life cycle

- Analytical method development

until this point, the compound has been in development for about three years and only one or two million dollars have been spent. This is spare change compared to the investment that will be made in a material that could be a potential champion.

Compounds that make it to Stage 3 will spend another six years in development. The process is likely to cost an additional $20 million to $40 million.

Going into development

A promoted compound will spend up to six more years in Stage 3 development and the process is likely to cost an additional $20 million to $40 million. This is a big decision and commitment for a company to make. Even at this stage, there are no guarantees of success. In fact, there are several ways the product can fail.

The material will go through mammalian toxicology studies, including a 90-day sub-chronic study, two-year rat studies and 18-month mice studies, reproductive and neurotoxicity studies and metabolism studies on rates, mice and crops.

Scientists will look at the environmental metabolism and fate of the material in soil and water. They will do ecotoxicology studies, including fish life cycle, avian reproduction and acute in fish, birds and invertebrates.

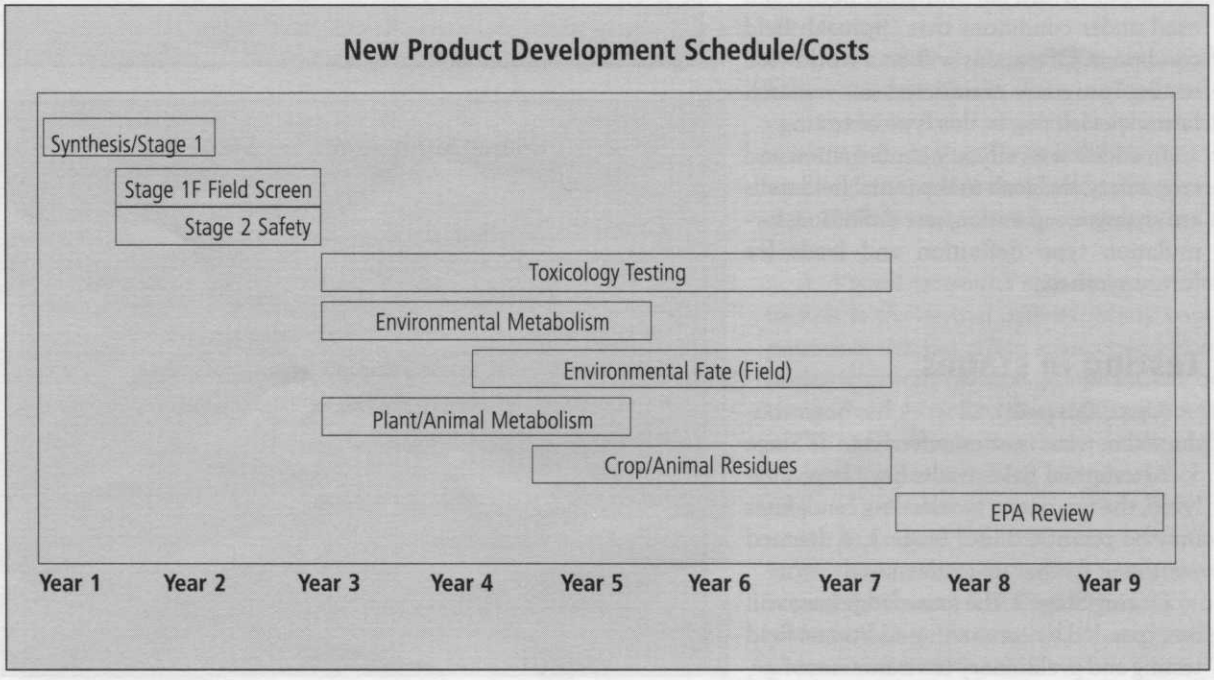
Once all of the studies are complete, summaries are assembled into an EPA dossier. A recent dossier submitted to EPA, for example, included 220 individual studies, draft labels, some 260 volumes of data and a Reduced Risk Summary Document. Talk about light reading!

Expedited EPA review process

The most realistic case is that it will take 24 months for EPA to review the package and register the product, assuming it gets expedited review status from the EPA.

The grounds for such a priority and expedited review are that the product qualifies as either a methyl-bromide replacement, is an organophosphate replacement or is a reduced risk product. A product can qualify for reduced risk status if the company can demonstrate that it:

* reduces the risk of pesticides to human



NEW PRODUCT DEVELOPMENT FACTS

- Total cost to register a new active ingredient is $25 to $40 million.
- More than 120 types of studies must be completed for registration.
- A typical Section 3 dossier is 25,000 pages or more in length.

health,

* reduces the risk of pesticides to non-target organisms,

* reduces the potential for contamination of groundwater or surface water or other valued resources or

* allows broader adoption of integrated pest management strategies by making such strategies more available or more effective.

Being granted expedited review by EPA is critical to a timely review. Otherwise, a material can languish in the approvals cycle.

During this time, the manufacturing company moves full speed ahead on designing internal training so company personnel know about the product, preparing outside user and distributor training and investing in all of the associated market positioning areas.

In general, Stage 1 takes 18 to 24 months, Stage 2 takes 18 to 24 months and Stage 3 takes 3 to 6 years. In total, it can take from seven to 10 or more years from the time a compound is first synthesized until it is registered by EPA.

Costly process

Next time you sign the invoice for a bottle of pesticide, keep in mind that the typical cost, just to complete the approval process, can be between $25 million and $40 million or more. Another $20 million to $100 million can be spent on manufacturing facilities.

More than 120 studies will be completed during that 10-year period. The result is known as a Section 3 dossier: a document typically about 25,000 pages long.

Tough as it all sounds, successful companies understand and appreciate that this process is required. They work to partner with the EPA, giving the government what it needs to make its decisions. They understand the limitations at EPA and try to resolve them or work within them.

By being open and honest – getting issues on the table early – it is possible to invest in safe and effective alternatives.

All of that time, energy, research and development is included in the bottle that you'll empty into the spray rig. The result, we hope, is profitable to the user, to the manufacturer and to society as a whole.

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