New Plant Growth Regulators: High Risk Investment?

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SUMMARY. Worldwide, plant growth regulators (PGRs) account for only 3% to 4% of the total sales of plant protection agents. This limited market potential, the rising costs of development and registration, and the demand for high profitability have created major constraints to the introduction of new PGRs. Conversely, PGRs have become an integral part of agricultural and horticultural practices and one might assume that the market is sufficiently lucrative to those companies active in this area. In the past decade, at least seven new PGR products have been introduced. In many cases, reduced requirements for registration have lowered the financial risks relative to expected profits.

Mineral fertilizers and chemical crop protection products have become indispensable in modern production systems, and it is well known that many disputes and conflicts result from this situation. Due to mounting public concern, regulatory guidelines for developing and using crop protectants have become increasingly restrictive. As a result of this change, the costs for developing a new product for crop protection have risen enormously over the last 20 years. It is generally accepted that the average costs involved to develop and introduce a new crop protection compound to the market are about \$130 million (German Crop Protection and Fertilizer Industry Association, 2000). Additionally, the time required from the discovery of an active ingredient to market introduction now covers a period of about 8 years. Not only must newly discovered compounds meet certain criteria, but existing crop protection agents must also be reregistered at regular time intervals. Furthermore, globalization and the demand for increased profitability has, in many aspects, forced the agrochemical industry into major restructuring. Companies, now more than ever before, must clearly justify the development of a new agrochemical product.

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The crop protection market is dominated by herbicides, insecticides, and fungicides. Out of about \$30 billion of annual sales worldwide (Agrow World Crop Protection News, 2001), PGR sales (including defoliants and desiccants) can be estimated to account for only about 3% to 4%. This realization is quite sobering when considering that expectations were much higher in the 1970s. At that time it appeared feasible to many experts that PGRs could be employed for regulating a wide range of plant processes, thus considerably improving the performance of crop plants (e.g., Weaver, 1972; Hardy, 1979). Consequently, substantial efforts have been made, both in academia and in industry, to translate these goals into reality. However, some 25 years later only a few of these ambitious intentions were realized.

- The PGR share of the pesticide market has increased only slightly.
- Relatively old products such as ethephon, chlormequat chloride, mepiquat chloride, and gibberellins represent the majority of the PGR market.
- Growth retardants still represent the majority of PGR sales.
- Very few companies are still engaged in searching and developing new PGRs.

It is the objective of this paper to summarize the economic aspects, risks, and opportunities of new PGRs. Reference is made only to chemically defined active ingredients. Complex extracts or preparations containing microorganisms are not dealt with. Related contributions have been presented by Crovetto and Shafer (1989), Baylis (1990), and Rademacher (1993).

General risks and challenges with developing PGRs

Recently, many companies have drastically reduced their activities in the PGR arena. The reasons for this reduction are manifold.

- Identifying PGRs for new uses is very difficult. It is, for instance, virtually impossible to perform mass screening for yield- or quality-enhancing compounds. Assays employed for selecting such compounds have to be rather indirect and thus face a high risk of failure.
- Developing a new PGR, especially for a new use, is far more laborious and cost-intensive than launching, say, a new herbicide for a standard use. Typically, far more trials must be conducted before label directions for use can be specified.
- To ensure successful market introduction of a PGR, a high level of technical training is required for internal personnel (e.g., sales representatives) as well as for external advisers and customers.
- Under practical conditions, factors difficult or even impossible to control (e.g., adequate dosing or weather conditions) may have a negative impact particularly on a PGR's performance. Resulting from this, the risk of litigation and crop compensation is above average.
- A good portion of the potential market is already saturated with existing products. Compounds such as chlormequat chloride or ethephon perform satisfactorily at competitive prices and thus render the introduction of new chemicals relatively difficult and unattractive.
- Because of the rigorous testing and technical expertise necessary in discovering and developing a PGR, one might assume that the capital expenditure required is well above that for the average pesticide. This is coupled with the fact that the actual market potential for a new PGR is difficult to estimate. In essence, predictions on the economic performance of a candidate compound may be relatively risky.
- Registration requirements have created a severe bottle neck, both financially and time-wise. Furthermore, there is a need for high profits. As a result of internal competition for resources, candidate PGRs often suffer more than other newly discovered crop protection compounds.
- To be economically viable, a new PGR must have a sufficiently large market and/or be sold at a sufficiently attractive price. As a consequence, the industry has to concentrate its efforts on uses in big crops and cash crops, which are primarily represented by wheat (*Triticum aestivum*), rice (*Oryza sativa*), barley (*Hordeum vulgare*), soybeans (*Glycine max*), sugar cane (*Saccharum officinarum*), cotton (*Gossypium* sp.), and fruits such as apples (*Malus domestica*), citrus fruits (*Citrus* sp.), and bananas (*Musa* sp.). Developing a new PGR for a minor crop may, in general, only make sense in conjunction with already having another attractive use.
- Certain targets for PGRs may also be goals for breeding, be it by conventional methods or by employing genetic engineering. For example, the availability of dwarf or semidwarf rice cultivars has clearly reduced the need for antilodging

compounds in most rice-growing countries.

Why are PGRs indispensable?

Over the last few decades PGRs have become integral parts of many horticultural and agricultural production systems. At least for the time being, it is difficult to imagine having acceptable alternatives to reducing lodging in intensive cereal production, controlling shoot height in ornamentals, steering fruit formation in pineapples (*Ananas comosus*), optimizing fruit set in apples, inducing parthenocarpic fruit formation in grapes (*Vitis vinifera*) and pears (*Pyrus communis*), stimulating latex flow in rubber plants (*Hevea brasiliensis*), or adjusting cotton, a woody perennial, to an annual production schedule.

Competition with plant breeding for some of these uses will continue to exist. However, even in spite of the possibilities that genetic engineering offers, it can still be forecast that PGRs will allow for a faster solution to many problems. Many years of breeding have, for instance, been only partially successful in introducing lodging-resistant cereal cultivars. Most importantly, PGRs allow plant growth and development to be actively regulated, thereby adjusting a given genotype to its particular growing conditions. In other words, PGRs can be used highly flexibly for the fine-tuning of plants, which grow at a given site under largely uncontrollable and unpredictable environmental conditions. It is unlikely that this will ever be achieved by any kind of breeding. Evidence is even available that several new, genetically engineered, cotton and rice cultivars require a higher PGR input as compared to standard varieties.

How to introduce new PGRs?

Recently, many companies in the agrochemical industry have withdrawn from PGR research, disillusioned about the prospects of this field. On the other hand, other companies have found their way to enter the market, maintain or even expand their PGR business. It is worth noting that at least seven new active ingredients have been introduced into practice over the last ten years (Table 1).

Hence, it is still possible to introduce new types of PGRs without taking unduly high risks. As far as can be judged, typical approaches for registration are as follows.

COMPLETE NEW REGISTRATION: TRINEXAPAC-ETHYL AND PROHEXADIONE-CALCIUM. Trinexapac-ethyl and

prohexadione-calcium are growth retardants of the acylcyclohexanedione-type. They block certain dioxygenases catalyzing the late steps of gibberellin metabolism by being structural mimics of 2-oxoglutarate, which is the cosubstrate of these enzymes (compare Rademacher, 2000). Trinexapac-ethyl has been developed primarily as an antilodging agent for small grains and for use as a turf growth regulator. Prohexadione-calcium is being commercialized as an antilodging agent for rice, cereals, and turf grasses grown for seed production. It is also used to control vegetative growth in fruit trees and ground nuts.

Both of these compounds had to be registered for use in edible crops, and one may assume that the full packages of toxicological and ecotoxicological studies were conducted. On the other hand, the market potentials and profitabilities of these compounds could be calculated with a relatively high degree of reliability, since the sizes of the different markets were fairly well known to the involved companies.

REGISTRATION OF AN ESTABLISHED PESTICIDE AS A PGR: QUINMERAC, TEBUCONAZOLE AND METCONAZOLE. Quinmerac was developed and registered for herbicidal use. Combined, for instance with metazachlor, quinmerac is being used to control grasses and some broadleaf weeds in sugarbeets (*Beta vulgaris*), oilseed rape (*Brassica napus* var. *rapus*), and other crops. Quinmerac possesses low auxin-type activity and, especially at higher rates, stimulates ethylene and abscisic acid formation in responsive plants (Scheltrup and Grossmann, 1995). Relatively low rates of quinmerac [10 to 80 g·ha⁻¹ (0.14 to 1.14 oz/acre) of active ingredient] were

found to increase fruit set in tomatoes (*Lycopersicon esculentum*) (Schott et al., 1989), and more importantly, improve fruit size and quality in several citrus species (Vilches and Pérez, 1996), olives, and peaches (Song et al., 2001). At present, quinmerac is commercially available as a PGR in Spain for use in citrus and olives and in South Korea for use in peaches. Additional uses in crops such as coffee (*Coffea arabica*) and registration in further countries are planned.

Selling quinmerac as a PGR in a few countries for use on citrus, olives, and peaches does not represent a large market. However, the vast majority of expenses required for registration was already covered by its herbicide use. Therefore, registration as a PGR was economically justified.

The situation is similar with the fungicides tebuconazole and metconazole, which were recently registered in some European countries as PGRs in oilseed rape. Like other triazole-type fungicides (compare Rademacher, 2000), both compounds possess growth-retarding activities. These products are of particular interest in winter oilseed rape, where excessive growth in a mild fall can be avoided, thereby increasing winter survival. In addition, both compounds are also being employed to reduce lodging in the same crop at later stages of development.

REGISTRATION OF NATURALLY OCCURRING COMPOUNDS: AMINOETHOXYVINYLGLYCINE (AVG). AVG is an inhibitor of ethylene biosynthesis and acts by blocking aminocyclopropyl-carboxylic acid (ACC) synthase, which converts S-adenosylmethionine into ACC, the immediate precursor of ethylene (Yang and

Hoffmann, 1984). The conventional synthesis of AVG is extremely complicated and expensive. However, AVG can be produced at more reasonable cost by fermentation of distinct strains of *Streptomyces*. This process, originally patented and developed by Hoffmann-La Roche in the 1970s (Pruess et al., 1974), was adopted by Abbott Laboratories (now Valent U.S.A.) who recently launched AVG in North America as a stop drop and senescence-delaying product for use in apples and pears (Shafer et al., 1996).

One important note is that naturally occurring compounds, such as AVG, may be registered at considerably lower cost and in less time than synthetic compounds. For instance in the U.S., many studies required for the registration of a chemical PGR are only necessary for a naturally occurring compound if the results from the earlier tier of testing suggest a potential issue or concern. One might assume that the waiver of such investigations was an additional argument for justifying the development of AVG.

REGISTRATION IN NONFOOD PLANTS: 1-METHYLCYCLOPROPENE (1-MCP).

Costs for registration, particularly for toxicological studies, are considerably less if the new compound is used exclusively in ornamentals or other plants not intended for food or fodder. Furthermore, registration in such niche markets is often assisted by programs such as IR-4 in the U.S.

Gaseous 1-methylcyclopropene is an ethylene antagonist (Serek and Reid, 2000). It has recently become registered in the U.S. for the preservation of cut flowers [distributed by Floralife, Inc. under license from Rohm and Haas Company, Philadelphia, Pa. (now part of Dow AgroSciences

Table 1. Recent introductions of plant growth regulators.

Active ingredient	Trade names ^a	Use
Trinexapac-ethyl	Moddus Primo Palisade	Antilodging in cereals and rice (<i>Oryza sativa</i>); growth control in turfgrasses; others
Prohexadione-calcium	Viviful Medax Apogee Regalis	Antilodging in rice, cereals and grass grown for seed; growth control in fruit trees and peanuts (<i>Arachis hypogaea</i>); others
Tebuconazole	Folicur	Antilodging in oilseed rape (<i>Brassica napus</i> var. <i>napus</i>)
Metconazole	Caramba	Antilodging in oilseed rape
Quinmerac	Bonus Jinsangpum	Increased fruit size in citrus (<i>Citrus</i> sp.), olives (<i>Olea europaea</i>), and peaches (<i>Prunus persica</i>)
Aminoethoxyvinylglycine	ReTain	Stop drop in apples (<i>Malus domestica</i>) and pears (<i>Pyrus communis</i>); improvement of fruit quality
1-Methylcyclopropene	EthylBloc	Delay of senescence in cut flowers

^aThere may be additional trade names.

LLC, Indianapolis, Ind.)). As far as is known, the compound will also be registered for use in edible fruits, for which additional studies would be required.

OLD COMPOUNDS WITH NEW NAMES AND IN NEW MIXTURES. Many existing PGRs are off patent and some are additionally exempted from registration. This situation has stimulated many minor manufacturers or distributors to launch me-too products under different brand names and, most often, at a minimum cost. For instance, gibberellins exported from mainland China are meanwhile available on the world market at remarkably low prices. An approach involving more innovation is the blending of two or more old PGRs into a new product. Such recipes have often created improved solutions in special situations.

Conclusions

PGRs have found their place in the production of arable crops as well as in horticulture and floriculture. One may assume that the market is sufficiently lucrative for those companies actively developing and selling PGRs. Relative to other types of plant protection compounds, the discovery, development, use, and commercialization of new PGRs are more complex and, typically, require a higher degree of experience, skill, and financial input. In order to be economically viable, a reasonable return on investment is critical. This goal may be reached by different approaches keeping in balance financial risks and expected profits. However, one must note that such procedures will not always be applicable.

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Companies

Syngenta (Basel, Switzerland)

Kumiai Chemical Industry Co., Ltd. (Tokyo, Japan); BASF AG (Ludwigshafen, Germany)

Bayer AG (Leverkusen, Germany)
BASF AG
BASF AG

Valent U.S.A. Corp. (Walnut Creek, Calif.)
Floralife, Inc. (Walterboro, S.C.)