THE IMPACT OF GENERIC HERBICIDES ON CROP PROTECTION

Pat Ryan, Strategic Development Manager at Syngenta Crop Protection UK Ltd., discusses the consequences of the ongoing growth in market share of generic herbicides at discussed at the recent BCPC Weeds 2001 conference at Brighton[1]

Introduction

Aging is the inevitable consequence of birth, as true for crop protection chemicals as it is for life. Traditionally, crop protection chemicals have been dominated by research-based, manufacturing companies. The increasing consolidation amongst such companies, the escalating cost of research and development and the patent expiry of chemicals discovered in the golden age of new active substance discovery during the 1970s and 1980s, has resulted in generic pesticides becoming the fastest growing sector of the agrochemical market. It has been assumed that the rate of growth of generic herbicide use during the last few years will be maintained in the future as:

- the number of herbicides losing patent protection increases
- farm incomes in Western Europe and the USA continue to reduce with a consequent increased scrutiny of input costs
- population and income levels continue to grow in less developed countries, with concurrent increases in food and food quality demands

Definition

The simplest way to define a generic pesticide is as one which is manufactured by a company other than the original manufacturer, whilst a generic manufacturer is, "a company, or division of a company, whose major activity consists of manufacturing the active substances of pesticides, the patents for which have expired, and for which it did not hold the original patents" (Hicks, 1994).

In 1996, patent-protected active substances accounted for 47% of the total global agrochemical market (Anon, 1998). Of the remaining 53% of agrochemical sales, only a relatively small proportion were manufactured by a generic manufacturer, even though these products were off-patent. It was estimated that approximately 10% of the total market was from generic manufacture.

It is anticipated that by 2005 the picture will be very different, with approximately 30% of global sales arising from active substances under patent, and 30% of all active substances being made by more than one manufacturer, *i.e.* generic – that is a growth in the off-patent market to $27.5 billion by 2007 (Anon, 1999). Paradoxically, however, the increasingly complex food chain requirements on farm outputs and the demands of regulatory authorities and non-governmental pressure groups will mitigate this growth and could cause the consolidation noted amongst R&D-based companies to be replicated amongst generic herbicide manufacturers and suppliers. The growth of generic pesticide use poses challenges and opportunities to: R&D-based companies, advise and service suppliers, farmers, processors and for product stewardship.

[1] This paper is largely based on the presentations and open discussion session at Weeds 2001, but all opinions expressed are, however, those of the author.

Selection of generic herbicides

New active substance development is driven by changing needs in sophisticated markets, *e.g.* Western Europe or by the potential for use against a global problem. In contrast the selection by generic manufacturers of which herbicides to produce is primarily based on retrospective analysis; there must be significant current sales either in global markets or highly profitable niche markets, the generic manufacturer must have the capability to manufacture the active substance to quality equal to that available from the former patent holder, (although ideally the compound is one which should also be difficult for other generic manufacturers to produce), the compound should be relatively cheap to produce as the manufacturer although not bearing the original discovery and development costs will need to recoup process development, plant installation, and regulatory investment, and the herbicide must not be liable to immediate substitution by new technological developments nor face significant regulatory uncertainty.

The key targets for generic manufacture have been herbicides, followed by insecticides and fungicides, with the leading generic crop protection product being Glyphosate with global sales in excess of $2 billion at end user level in 1997 (Hicks, 1998). Research conducted by Produce Studies Research, (Figure 1) (Anon, 1999) shows that this trend is set to continue, with herbicides remaining the main generic target.

The main herbicides currently being developed as generic pesticides (Anon, 1999) are given in Table 1.

Table 1. The generic herbicide market.

	($M) 1997
Imidazolinones	932
Sulfonylureas	925
Propionic acids	353

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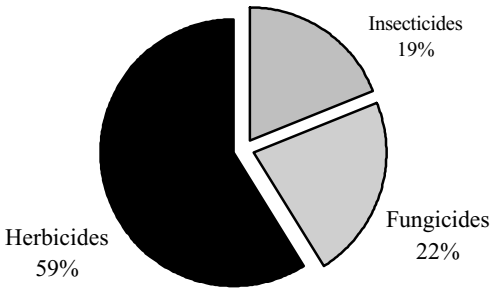

Figure 1. **Estimated split of new generics.**

Generic suppliers

There are three distinct types of generic supplier – manufacturers, third-party suppliers and parallel importers (Anon, 2000).

Manufacturers

Manufacturers make active substances and usually formulate products as well, often supplying their own packed material to the market. This is the category with the highest investment as production facilities are needed, and regulatory data are usually generated in order to obtain and defend registrations. All R&D-based companies produce off-patent products. As the generic market continues to develop rapidly, some of these companies have acquired major shareholdings in, or bought, established generic manufactures: for example, DowAgrosciences/Sanachem, AgrEvo/Stefes and DuPont /Griffin.

Third-party suppliers

Third-party suppliers buy active substances and/or products from another manufacturer to supply. Data may be generated on the formulated product, but the primary manufacturer will usually be relied upon for data on the active substance.

Parallel importers

Parallel importers simply buy packed products which are identical to those in the country into which they will be imported. The importer registers, imports and supplies such products under its own name. This requires no data generation other than proof of identicality.

Of the three categories, the third party supplier is the most numerous and may be sourcing products from a number of manufacturers, including generic manufacturers. As an example, of all the companies holding approvals of crop protection products in the UK, less than 10% are R&D-based companies, more than 75% are mainly third-party suppliers or parallel importers, and only approximately 15% are data-holding manufacturers of generic active substances.

Impact of generic herbicides

Cost

Marketing strategies for generic herbicides are based around either selling volumes of product at an acceptable profit above production cost ("cost-up") or maximising the value from an existing supply chain ("discounting"). Table 2 demonstrates how the entry strategy is shaped by the key market factors.

Depending on the supply chain, and the existence of an appropriate marketing channel, the "customer" may be an end user, third party supplier or a distributor. The classic scenario is where one or more generics compete alongside the branded product to any given customer. In most cases generics are offered at a discount to branded products. This is the usual method of overcoming the image of security that a branded product has developed. Typically, a "cost-up" strategy will cause a crash in the price of a branded product whilst a "discount" strategy will result in a slow erosion in price of the brand.

Generics may be traded purely at an operating margin above manufacturing cost, an approach leading to rapid and dramatic value reduction. Obviously lower-cost inputs are welcomed by all end-users, but low margins for manufacturers often result in reduced investment and deterioration in the product offered on farm.

Availability of active substances

As the R&D companies continue to merge, they are being forced to divest active substances to avoid market monopolies. Such active substances may be acquired by major generic manufacturers which have the resources to develop these acquisitions and a desire to add an R&D-based offer to their product portfolio. An example of this is the global acquisition of propaquizafop by Makhteshim-Agan following the merger of Novartis and Zeneca.

In addition, active substances registered in or before 1993 are being reviewed by the European Commission (Anon., 2001). A significant number will not be supported by crop protection companies because the costs of generating data required cannot be justified in terms of sales within the EU. Those active substances that are unsupported will be withdrawn in July 2003. It is anticipated that up to 50% of

Table 2. Influence of market factors on entry strategy for generics.

Patent expiry	Market size	Production	Original patent holder response	Generic entries	Generic strategy
Global	Large	Easy, low cost	Aggressive	Many	Cost-up
Global	Large	Difficult, expensive	Tolerant	Few	Discounting
Regional	Small	Easy, low cost	Tolerant	Few	Discounting
Regional	Small	Difficult, expensive	Tolerant	One	Discounting

the active substances currently approved in the EU will disappear during the Review process. This will have a significant impact on minor uses (Wise, 2001; Knott, 2001), mainly in horticulture but also in larger area crops and forestry. For example, it is possible that there will be no pre-emergence herbicides available for use in peas produced in the UK for quick-freezing and canning. Manufacture of some unsupported active substances may continue for markets outside the EU. Derogation may be granted by the EC for essential uses of some of these particular herbicides for a short period in order to allow time for alternative weed control measures to be developed; see Orson and Thomas (2001) for generic herbicides that are likely to be withdrawn from the EU in 2003 unless derogation is granted.

Some active substances not supported by the original manufacturer are being defended by a generic manufacturer. In these cases, the future of some products valued for offering alternatives, *e.g.* for resistance management or as a sole use in a minor crop are in the hands of generics. Of the 318 active substances notified in the EU Review, more than 30% are being supported by more than one company, *i.e.* are generic active substances. Some of the data needed to support important active substances will therefore be provided by generic manufacturers. The major generic suppliers are also often highly active in further developing herbicides in the light of changing farmer needs. The generic supplier can therefore further invest to develop the product into new crops and uses, allowing the generic product to have a more comprehensive label than the original product.

No general statement can be made about the quality of active substances and products produced by generic manufacturers. In many cases, the active substance is of identical purity to that from the original manufacturer. Quality is seldom an issue in the developed world, but in less developed countries, although apparently satisfactory regulations are usually in place, policing of conformance can be inadequate leading to potentially serious problems for farmers and the community.

Supply industry effects

The supply industry (distributors) have to work against a background of an arable agriculture operating at the lowest level of profitability since the 1930s. The supply industry has responded to these changing circumstances by major restructuring which is still continuing. As with the R&D-based manufacturers, which in its heyday consisted of 20 major R&D companies, now reduced to 6 or 7, the supply industry has seen a rationalisation where the industry is increasingly dominated by a small number of often multinational companies

From the supply industry's perspective, product choice is now limited to those supplied by a small number of R&D-based companies selling a range of novel patented products, and to an equally small number of other suppliers who either manufacture generic products or who parallel import products from countries when the exchange rate is favourable. In most situations the distributor's portfolio contains a balance of patented, generic and parallel import products.

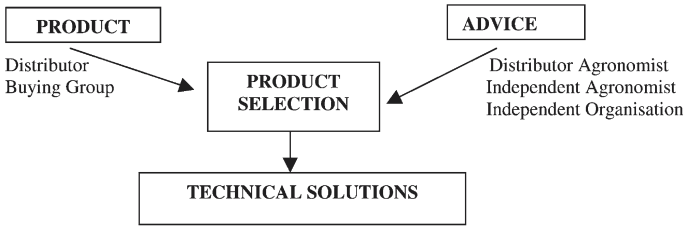

Figure 2. **Choices available to the farmer in the solution of crop protection problems.**

Effect of generic products on on-farm advice

The farmer has a choice of many routes by which he can solve his crop protection problems (Figure 2).

Generic products will have been used for many years, and are understood by agronomists and increasingly trained and competent farmers and spray operators. Some manufacturers will seek to maintain technical advantages by providing updated technical information, and this may give them a commercial edge.

There may, however, be an impact on technical support and training provided to advisers and distributors. Traditionally the major manufacturing companies have provided technical training on the best use of their products and in particular on product stewardship matters such as resistance management and environmental protection. Without the resources of R&D-based companies or multi-national generic manufacturers to carry out or sponsor such work, and promote the technology transfer, it is likely that such programmes will be adversely affected. Crop assurance, processor and supermarket protocols are increasingly impacting on farmers' choice of products. These are prescriptive of which products may be used, using brand or active substance names. Generic manufacturers will increasingly have this additional hurdle to climb after being granted approval.

Agronomic factors affecting the current and future use of generic herbicides

Many current generic pesticides were instrumental in the rapid development of today's farming systems. Effective herbicides allowed farmers for the first time to grow crops on land most suited for their production. No longer do crops have to be grown solely for their contribution to weed control through the rotation. There are however, issues that will influence the future usage of generic herbicides.

Relevance to current and future cropping systems

Many generic herbicides have witnessed a decline in usage as more effective and appropriate herbicides are introduced (Orson and Thomas 2001). It is unlikely that cropping systems will return to those that enabled the effective exploitation of herbicides such as 2,4-D and dicamba. Current systems often encourage weeds that are not controlled by older herbicides – indeed it can be suggested that the usefulness of a herbicide declines with age, that is issues created by the very success of a herbicide can over time lead to a restriction of its use due to, for example resistance development or environmental impact.

Naturally, where a generic herbicide is relatively cheap for the farmer to use, fits in with the current usage of labour and machinery and is very effective and currently used on a large scale such continued widespread use is relatively assured in the medium term.

Herbicide resistance

Generic herbicides offer alternative modes of action and hence may play an important role in the prevention of the development of herbicide resistance. A few herbicide modes of action dominate weed control and there is particular concern over the increased usage of the sulfonylureas across a range of crops. For instance, target site resistance to this mode of action is now widespread in common poppy in northern Mediterranean countries and generic herbicides such as bromoxynil and ioxynil with mecoprop have an important role in the control of these resistant stocks.

Herbicide-tolerant crops

Those generic herbicides that provide effective and cheap broad-leaved weed control in the non-major crops such as oilseed rape and sugar beet may continue in the medium term to be used on a wide scale. This is partly because in these crops, herbicide tolerance to non-selective herbicides may be introduced, reducing further the incentive of companies to develop selective alternatives. Hence, in oilseed rape and sugar beet, herbicides such as chloridazon, lenacil and metazachlor may continue to be used at current levels until the introduction of herbicide tolerance to glyphosate or glufosinate. However, the lack of incentive to develop selective herbicides for broad-leaved crops will reflect on future options in minor broad-leaved crops that may not be subject to genetic modification.

Responses from R&D-based companies

Innovation in crop protection can be described by a classic model of technology 'push' and market 'pull'. We are participating in an era where factors in both 'push' and 'pull' are changing faster than ever before. This creates greater tensions within the innovation model and leads also to greater uncertainty in the future.

A potentially successful, but difficult to accomplish, strategy for R&D-based companies is to move from simply introducing new active substances, towards the following:

- The discovery of novel active substances which provide key benefits over the state-of-the-art. These benefits are increasingly not only performance related (more highly active molecules with a new mode of action) but are also influenced by customer needs for improved flexibility, safety and environmental characteristics.
- Performance enhancement of existing active substances by modulating its delivery to the biological target. This may frequently be through formulation technology, but also through improved application methods or combination with other control measures in integrated crop management.
- The development of crop solutions which are tailored to meet the needs of specific customers or customer categories. This becomes feasible with more comprehensive data-systems together with more holistic and deterministic models of product performance integrated into the overall cropping system.

Such a strategy is based on the assumption that there is a need for new solutions to existing problems and new customer needs. Old generic products will be replaced by modern, more desirable alternatives. Government regulations will limit the use of old-generation products. Farmers will seek to maximise their profits through tailoring solutions to individual needs, and the customer base changes as food processors, retailers and consumers desire more knowledge on the provenance of agricultural produce. Technological advances underpin such a research strategy. The most dynamic areas of technology change are in functional genomics, xenobiotic interactions and bio-information systems. The synergy between these combined areas provides powerful new tools to enhance understanding of crop protection, bring novel products to the market and use these products more effectively, for example, in precision agriculture.

Although products which result from a combination of all the described technologies are still to appear, recently introduced active substances demonstrate success in at least some components of the strategy. For example, metolachlor was introduced into the market in 1976 as a racemic mixture of four isomers, the two *S*-isomers giving the greatest herbicidal activity. Intensive biological evaluation has shown that equivalent herbicidal activity in the field can be achieved with a 35% reduction of application rates compared to the racemic form of metolachlor (O'Connell *et al.*, 1998). The introduction of *S*-metolachlor from 1977 effectively denied the opportunity for generic metolachlor due to the racemic mixtures lower use rate, reduced chemical load in the environment; reduced packaging needs; reduced shipment costs; less wastes in production and increased application efficiency for the grower.

This product replacement has been further supported by the introduction of variable rate application systems – adding services to a herbicide to further distinguish it from potential generic competitors.

Conclusion

There is no single globally relevant conclusion to the impact of generic herbicides on crop protection.

Generic products account for some 35% of agrochemical sales worldwide, but only about 15% in Europe, reflecting the contrasting opportunities and issues in highly developed and less developed countries. Paradoxically, generic manufacturers face greater challenges than the R&D-based companies. In more developed countries, regulation, food chain and society expectations favour new active substances over generics and are more at ease with the strategies being adopted by the R&D-based companies. In less developed countries, there will be a continuing and growing need for the availability of products where price is the key determinant, however, as living standards rise accompanied by local pressures for sustainability and environmental protection, and regulatory imposition by export markets

there is likely to be a shift towards more sophisticated herbicides.

However, significant opportunities exist for those generic manufacturers who can move from a complete reliance on price sensitive, commonly available active substances to the production of newly off-patent materials offered with additional services and guarantees of quality. Indeed this is a strategy that the established generic manufacturers will need to pursue if they are not to be drawn into destructive competition with the extreme low cost and often low quality producers from South East Asia.

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References

Anon. (1998). AGROW (30/1/1998).

Anon. (1999). The World Market For New Generic Agrochemicals – post 2000. Produce Studies Research and Enigma Marketing Research.

Anon. (2000). Wood Mackenzie Research, International Crop Protection Report 2000, prepared for Makhteshim-Agan Industries (2000).

Anon. (2001). The EU Review Programme. *Pesticide Outlook*, **12**(3), 121-122.

Butchart, J. E. (2001). The impact of generic herbicides on on-farm advice. *Proceedings of the BCPC Conference – Weeds 2001*, **1**, 117–122

Hicks, B. R., (1994) Generic pesticides – The companies. PJB Publications Ltd .

Hicks, B. R., (1998). Generic pesticides – Changing roles and changing fortunes. *Pesticide Outlook,* 33–38.

Knott, C. (2001). The outlook for minor pesticide uses in the UK and Europe. *Pesticide Outlook*, **12**(6), 224–228.

Nevill, D. J.; Quadranti, M.; Leadbitter, N.; Sadler, D. (2001) A research strategy to drive sustainable innovation in the herbicide market. *Proceedings of the BCPC Conference – Weeds 2001*, **1**, 99–106

O'Connell, P. J.; Harms, C. T.; Allen, J. R. F. (1998). Metolachlor, s-metolachlor and their role within sustainable weed management. *Crop Protection* **17**(3), 207–212.

Oliver, S G (1998). Systematic functional analysis of the yeast genome. *Trends in Biotechnology* **16**, 373–378.

Orson, J. H.; Thomas, M. R. (2001). Impact of generic herbicides on current and future weed problems and crop management. *Proceedings of the BCPC Conference – Weeds 2001*, **1**, 123–132

Sisson, A. M.; Williams, R. O. (2001). The benefits of generic products to the market. *Proceedings of the BCPC Conference – Weeds 2001*, **1**, 107–116

Wise, C. (2001). Loss of herbicides for minor crops – impact on European Growers. *Proceedings of the BCPC Conference – Weeds 2001,* **2**, 817–824.

Organic farming and biodiversity

Dutch researchers, led by David Kleijn and Frank Berendse at the Nature Conservationand Plant Ecology Group, Wageningen Agricultural University, The Netherlands, claim that agri-environment schemes do not effectively protect biodiversity in the Dutch agricultural landscape (*Nature,* 2001, **413**, 723).

The researchers claim that a large 'green farming' project in the Netherlands, which had been designed to benefit wildlife, has not worked. For 20 years, Dutch farmers have been paid to delay the spring mowing of their grass fields until June, to encourage birds to nest and hatch their chicks in safety. Kleijn and Berendse compared bird life on 78 fields managed in this way with nearby fields managed conventionally. They found "no positive effect on bird species diversity". In fact, most common birds, such as oystercatcher, black-tailed godwit, lapwing and common redshank, nested less often in fields with agri-environmental schemes, perhaps because the soils contained fewer earthworms to eat. There was no positive effect on plant species richness, although hover flies and bees showed modest increases in these fields. Kleijn believes that this and similar environmental management systems which have been introduced across Europe, are flawed because they fail to understand the complexity of ecosystems.

These Dutch findings conflict with the much-publicised 6-year organic apple orchard studies from John Reganold of Washington State University, also published in Nature (Nature, 2001, 410, 926), which claimed that organic orchards are not only more profitable and produce tastier produce than conventional ones, but are also better for the environment, bringing about an improvement in soil quality and other environmental quality indicators.

A UK Government report on the future of English farming, amongst its recommendations, encourages an increase in organic and sustainable farming. The independent report, published by the Department for Environment, Food and Rural Affairs (Defra), which examines issues relating to the entire food chain, and has been welcomed by environmental groups. For further information on this report whose authors were chaired by Sir Donald Curry see http://www.cabinet-office.gov.uk/farming/, from where the report can be downloaded.