

When is an off-patent product not a generic?

Dr Nigel Uttley of Enigma Marketing Research looks at the balance between proprietary and off-patent products and examines the split between generic and proprietary off-patent products

Defining the difference between generic and proprietary products is not always easy in the world of agrochemicals.

A proprietary product has a granted patent in force but, once the patent has expired, the product can be classified as generic or proprietary off-patent. A true generic product is where the generic company has registrations (approvals to sell) products that are independent of the inventor company's data. A proprietary off-patent product exists when there is no stand-alone competitor(s) to the inventor company.

But how does this proprietary off-patent situation arise and why is there no generic competition? Firstly, it is necessary to look at the balance in the industry between the R&D-based sector and the generics sector. In order to do this, we need to consider the key issues of intellectual property (IP) rights and registrations and their effect on market exclusivity.

R&D into new active ingredients and, more recently, genetic modification has been the basic driver of the agrochemicals industry for the last 50 years and has resulted in the development of more and more sophisticated products. Today, added performance from new products tends to be targeted at one of the following areas:

- Better control of resistance, mainly for fungicides but also increasingly for herbicides and insecticides
- Improved crop yield
- Simpler usage - for example, a reduced number of applications
- Safer and more environmentally friendly actives
- Reduction in metabolites

In addition, active ingredients which are safer to use, more environmentally friendly and impart specific biological effects will continue to be developed, initially for the more sophisticated markets of North America, Europe and Japan.

It takes, on average, ten years from discovery to registration for an agrochemical product. During this time, the product's toxicological, environmental and efficacy profiles are established and production scale-up and regulatory affairs work activities are carried out.

Some 50,000 products will have been screened and discarded for the one that achieves commercial launch and the

Table 1 - Patent status of List 1, 2 & 3 & New Active Substances

List	No. of products in list	Proprietary products	Off-patent generic products
1	60	0	60
2	30	6	24
3	155	10	145
NAS	135	81	54
Total	380	97 (25.5%)	283 (74.5%)

cost of this exercise is put at about €180 million. In spite of this continued investment and discovery techniques such as combinatorial chemistry and high throughput screening, the number of new chemical entities (NCEs) reaching the market has declined (Figure 1).

Has this decline in NCEs resulted in a declining market share for the R&D-based companies? For the time being, the answer to this question seems to be 'no', as the top six agrochemicals companies still have a global market share well in excess of 70%, even though they have an increasing portfolio of off-patent products.

How is this achieved? Registration issues and IP rights are the key to market defence strategies in a post-patent scenario. Although this article primarily analyses the EU situation, the fundamentals of registration issues and IP rights are similar in the EU to the US and other developed countries.

Registration issues

In order to obtain an approval to sell an agrochemical in the EU, it is necessary to comply with EU Directive 91/414, the Plant Protection Products Directive. This requires the active substance (AS) to be approved at EU level (this is referred to as Annex I status) and then to seek approval at the Member State level for the formulated product (Annex III status).

Several hundred existing actives have had to undergo a re-registration process in order to comply with the stricter requirements of 91/414. The main commercial products were divided into three Lists, numbered 1, 2 and 3.

Interested parties have to submit AS dossiers, which are then assessed for completion. Once a dossier is declared complete, its owner becomes a Main Data Supplier and elects for certain data to be classed as protected.

This protected data receives a five-year period of protection from the date it enters Annex I. Once a product is on Annex I and the protected data studies are known, a generic applicant has one of three basic options.

Unlike in pharmaceuticals where it is only necessary to prove bioequivalence, the applicant can generate his own data package, with the exception that mammalian toxicology studies cannot be duplicated and therefore access to these has to be negotiated with the data holder. In practice, this appears to be equitable, since primary data holders recognise the need for transparency in this sensitive area.

Alternatively, he can negotiate access to a complete data package. Again, mammalian studies are not a problem but environmental studies are not under the same public scrutiny

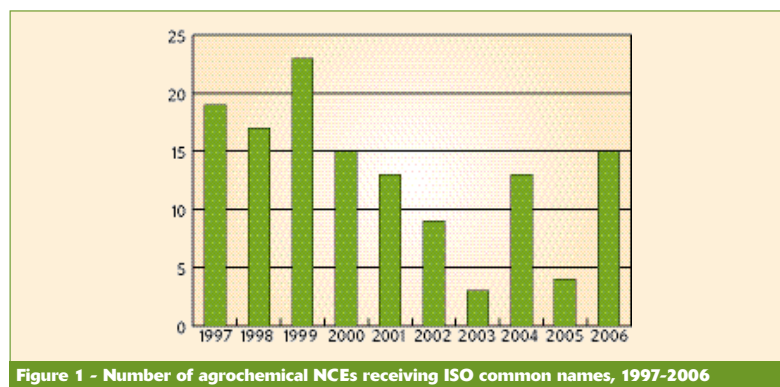


Figure 1 - Number of agrochemical NCEs receiving ISO common names, 1997-2006

and the primary data holder has a considerable negotiating advantage. With no arbitration system in place, it is often difficult for the generics company to strike a practical and economic data compensation deal.

Otherwise, the applicant can wait for the five years of data protection to expire. This period is now complete for certain products; for example 2,4-D data protection expired on 1 October 2007.

So does EU Directive 91/414 extend market exclusivity in a similar manner to patents and what has been the effect of this on market dynamics? Assessing the ASs on Lists 1, 2 and 3 plus the new active substances (NASs) entering the market since the introduction of 91/414, we can see from Table 1 that nearly 75% of all of these are off-patent.

Now consider only List 1 ASs, which are all off-patent, and assess the effect of 91/414. These ASs can be divided into two categories. In Category 1, there are 25 ASs where a task force or more than one main data supplier was identified as the main data supplier. Thus genuine competition exists and these off-patent products can be described as generic.

However in Category 2, 35 ASs only have one data supplier or all additional submissions to the main data supplier were withdrawn - primarily due to lack of data. Thus, for these off-patent ASs a market exclusivity or proprietary scenario exists.

Thus nearly 60% of off-patent products on List 1 are not generic and therefore fall into the category of proprietary off-patent products. In this way, the EU registration system provides market exclusivity for many old ASs and provides one of the reasons why an off-patent product is not a generic.

IP rights

The active ingredient may no longer have patent protection but potential generic competitors will need to establish whether ancillary patents exist that would restrict the freedom to operate.

In addition to the basic patent which protects the molecule *per se*, there may be other patents covering novel formulations, synergistic mixtures of active ingredients, methods of manufacture, key intermediates or the resolution of a racemic mixture to the optically active isomer.

Mixtures of agrochemical ASs are commonly used and they are either pre-formulated or tank-mixed just prior to application. One of the major ways a market can be protected against generic competition is to segment the market through mixture products.

Often the mixture active substance is patent protected or is a proprietary off-patent product. In addition, many combina-

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tions of ASs have also been patented and the validity of these patents has not been challenged by the generics sector.

The UK tebuconazole market is a good example of market segmentation by mixture products. Here, 26 products are registered for straight (i.e. not mixed with any other active ingredient) tebuconazole.

Of these, four are held by Bayer CropScience, the innovator company, the remaining 22 by 14 other companies. Thus the straight tebuconazole market is a true generic market. However, there are 13 mixture products containing one or more additional ASs.

Of these, three ASs are generic and registrations other than Bayer's exist, meaning there is real competition in the marketplace. The other ten are proprietary patented or proprietary off-patent; only one non-Bayer registration exists, which is held by Syngenta. Thus, Bayer CropScience has successfully segmented the total tebuconazole market by creating proprietary mixture products and restricting generic competition.

Agrochemicals v. pharmaceuticals

The crop science market, consisting of crop protection and related chemicals, bioscience and non-crop applications, but excludes €8 of conventional seed sales has a global value of almost €39 billion/year.

The pharmaceuticals industry, comprising prescriptions and related categories (OTC, diagnostic agents and some nutritionals), is over ten times larger, at €400 billion/year. Indeed, the combined sales of Novartis and Merck or those of Pfizer and Teva, the leading generics firm, are both slightly more than the size of the total crop science market.

As Table 2 shows, there is a clear contrast in the relative dominance of the top players, with the largest six agrochemicals firms having 78.1% of the market in 2005. The top six in pharma had only a 33.6% share. The top six generic agrochemicals companies also have a much higher combined share than the top six generic pharmaceuticals firms: 13.1% v 4.3% (Table 3).

There are also many other similarities and differences worth highlighting. In both industries, patent term extension and Supplementary Protection Certificates exist, resulting in patent terms of up to 25 years. However, the Bolar provision, allowing product registration work to be carried out during the life of the patent, exists in most countries for pharmaceuticals but not for agrochemicals.

In both industries, R&D is a very significant cost as a percentage of revenue. In general, however, healthcare spending is a major political issue and many governments have a vested interest in creating a more competitive environment in order to reduce prices. This is not the case for agrochemicals.

Data protection periods for new and old products in effect extend the patent life or market exclusivity period in both industries. For pharmaceutical products, the 1984 Hatch-Waxman Act allowed generic applicants to provide an abbreviated new drug application (ANDA) to prove that its product is bioequivalent to that already approved, thus negating the requirement for clinical trials.

This was a huge incentive for generic pharmaceuticals companies that resulted in a steady increase in the proportion of prescriptions being issued for generic drugs, from under 20% at the time of the act to over by 50% by 2002. In the US and EU, however, generic agrochemicals companies have to provide a full data pack - proving bioequivalence is not sufficient.

Clearly, then, there is greater encouragement to invest in new products for generic pharmaceuticals companies than for generic agrochemicals companies. This is one major reason why the top six R&D-based agrochemicals companies dominate the market.

Table 2 - Top six agrochemicals & pharmaceutical companies by sales, 2005

Top 6 agrochemical companies		Top 6 pharmaceutical companies	
Company	% market share	Company	% market share
Bayer CropScience	19.2	Pfizer	8.2
Syngenta	16.6	GlaxoSmithKline	6.2
Monsanto	16.6	Novartis	5.2
BASF	10.8	Sanofi Aventis	5.2
Dow AgroSciences	8.8	Johnson & Johnson	4.4
DuPont	6.1	AstraZeneca	4.4
Total	78.1	Total	33.6

Table 3 - Top six generic agrochemicals & pharmaceutical companies by sales, 2005

Top 6 generic agrochemical companies		Top 6 generic pharmaceutical companies	
Company	% market share	Company	% market share
Makhteshim-Agan	4.0	Teva	1.4
Nufarm	3.2	Sandoz	1.1
Arysta	2.4	Ratio Pharm	0.5
Cheminova	1.6	Watson	0.5
Sipcam	1.0	Merck KGaA	0.4
United Phosphorus	0.9	Mylam	0.4
Total	13.1	Total	4.3