Post-Patent Outlook

Just because you *can* doesn't mean you *should*: Why patents, data, and market share are better guides for product development than technical expertise and ability to manufacture.

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Editor's note: This analysis is an excerpt from Enigma Marketing Research's latest report, "What Happens to the Market After an Agrochemical Patent Expires?", which analyzes the extent to which the generic sector has penetrated markets following AI patent expirations. The report examines post-patent defense strategies and identifies opportunities for product development and market access. For more detailed information, visit www.enigmamarketingresearch.com or contact the author at nigel.uttley@enigmamarketingresearch.com.

Most analysts put the generic companies' share of the total crop protection market at 25% to 30%, yet EMR's analysis shows that, for the 88 AIs profiled in our report, generics have only captured 11% of the market. For the older AIs with pre-2000 patent expiry such as 2,4-D, acetochlor, chlorothalonil, chlorpyrifos, deltamethrin, glufosinate, glyphosate, lambda cyhalothrin, mancozeb, and paraquat, the generic sector has had much greater success.

The development of mixture products has been a key strategy in defending a market from generics. Many mixture patents have been granted in the last 10 years to 15 years and, in addition to the technical benefits of mixture products, commercial benefits also result.

For example: Mixtures segment the market creating a greater number of branded products making it harder for generics to take market share.

Use of patent protected AIs limits market entry by generics — if one of the mixture AIs is patent protected, generic companies will not have access to this AI and therefore cannot enter this segment of the market until all intellectual property rights (IPR) have lapsed.

Many mixture products have received patent protection in their own right resulting in extended patent rights beyond the expiry of the AI.

Bixafen is a good example of a partner AI that still has patent protection and therefore all mixtures containing bixafen are patent protected. The basic bixafen patent expires in 2023, and major mixture products exist, such as with:

- fluoxastrobin
- fluoxastrobin + prothioconazole
- prothioconazole
- tebuconazole
- prothioconazole + spiroxamine
- prothioconazole + tebuconazole

All of these will have patent protection to at least 2023, and in the EU, many supplementary protection certificates (SPCs) exist for these mixtures extending protection well beyond 2023.

The development of mixture products and the associated IPR has provided inventor companies with significant additional market protection as the following example of prothioconazole demonstrates.

Prothioconazole was first launched in 2005, and it was marketed in all major markets by 2016. The EU market is particularly important, and prothioconazole is mixed with many other actives, including:

- bixafen
- bixafen + fluoxastrobin
- bixafen + spiroxamine
- bixafen + tebuconazole
- bixafen + fluopyram + tebuconazole
- fluopyram + tebuconazole
- fluopyram
- fluoxastrobin
- pencycuron
- spiroxamine
- tebuconazole
- triadimenol + triazoxide

A number of patents exist to these mixtures, and SPCs have been granted extending market protection to well beyond the expiry of the AI patent. The basic patent for prothioconazole expires in 2015, but SPCs extend this to 2018. In addition, 12 mixture products also have additional patent and SPC protection extending market exclusivity from 2019 to 2026.

The EU is a very large market for prothioconazole, and over 80% of the value of this market is for mixture products and thus, generic entrants will find it very difficult to take significant market share for a number of years to come.

Table 1
Examples of AIs with SPCs

Active ingredient	Expiry year of basic patent	Expiry year of most SPCs
boscalid	2012	2017
iodosulfuron	2012	2015
topramezone	2016	2020

Source: Enigma Marketing Research, "What Happens to the Market After an Agrochemical Patent Expires"

Supplementary Protection Certificates

The basic patent or primary patent covers the discovery of the AI, its uses as a single active ingredient and/or in mixtures, formulations of the AI, and how it is manufactured.

SPCs for plant protection products came into effect from Feb. 8, 1997 and run to a maximum of 15 years from date of first marketing authorization in a European member state but for no more than five years after the 20-year patent term expiry.

It is essential that any company planning to enter the EU market must establish whether patents for the active ingredient, mixture products or other secondary patents have expired, including whether SPCs were granted and their current status.

Marketing/Licensing Deals

In many instances, inventor companies license AIs to other companies in order to achieve greater market exposure and to develop new products through mixtures. This is especially so for Japanese inventor companies.

Metconazole, for example, was discovered by Kureha and initially co-developed with AgriShell (now BASF) to control a range of fungal infections including *Alternaria*, *Fusarium*, *Septoria* and rust diseases on cereals, canola, rice, maize, soybeans, sugar beet, cotton, stone fruit, nuts, peanuts, ornamentals, and turf.

Kureha is a relatively small R&D-based company and has limited in-house marketing capabilities to cover all the major markets for metconazole and therefore entered into a number of collaborations with other companies such as:

- Sumitomo Chemical (including its U.S. subsidiary, Valent)
- BASF for foliar uses of metconazole in North America on small-grain cereals, soybeans, sugar beet, and cotton.
- Nippon Soda launched metconazole in Japan as a mixture (+ thiophanate-methyl).
- BASF launched metconazole as a mixture, TwinLine (+ pyraclostrobin) in the U.S. for use on wheat, barley, oats, rye, and triticale.
- BASF gained approval for metconazole as Tectura (+ boscalid) in the UK for use on canola/oil seed rape.
- BASF launched metconazole as Osiris (+ epoxiconazole) for use on cereals.

Thus collaboration has not only achieved wider geographical usage of metconazole but has also resulted in license companies developing mixture products and expanding metconazole's use spectrum.

Benthiavalicarb-isopropyl was discovered by Kumiai Chemical and developed for use on vegetables, potatoes, and grapevines. Kumiai has entered into a number of collaboration with other companies such as:

- Staehler (now FMC) launched benthiavalicarb in Switzerland in 2004.
- Makhteshim-Agan (now Adama) launched benthiavalicarb in Cuba in 2004.
- Adama launched the mixture product, Vincare (benthiavalicarb + folpet), in a number of markets
- Certis Europe launched benthiavalcarb as Valbon in Italy.
- Nulandis launched benthiavalicarb in South Africa as Valbon (+ mancozeb) for use on potatoes and grapes.

Again, collaboration has not only achieved wider geographical usage of benthiavalicarb but has also resulted in license companies developing mixture products and expanding benthiavalicarb's use spectrum.

Registration Requirements and Data Protection

Each country/region has a different registration system and within most systems, there is a provision for data protection. The most complex registration system is undoubtedly that of the EU, and the protection periods vary depending on the type of authorization issued. A third party cannot use protected data to support an application for authorization.

Table 2 shows examples of how data protection has extended market protection well beyond the expiry of the 20-year patent term for various AIs.

Only Fools Rush In

To successfully develop a new generic agrochemical, a company requires deep pockets, a multi-disciplinary team, forward planning and above all a management team focussed on the long term. There have been many examples of an AI coming off patent and resulting in an eruption of manufacturers who know they can produce it but not where and how to sell it. Take pyrimethanil as an example.

Pyrimethanil is a anilinopyrimidine fungicide discovered and developed by Schering (became AgrEvo, then Aventis, now Bayer CropScience) to control fungal diseases such as grey mold, leaf scab, and brown rot on a wide range of crops including almonds, pistachios, grapes, peaches, nectarines, apricots, pome fruits, plums, potatoes and other tuberous and corm vegetables, bulb vegetables, tomatoes, strawberries, and raspberries.

The European and other patents expired in 2007. Pyrimethanil is sold in most of the major markets in the world, and global sales of pyrimethanil based products reached over $70 million, and the generic sector has less than 10% of this market. Yet more than 20 companies claim to manufacture pyrimethanil. It is highly unlikely that all are manufacturers, but it demonstrates how an AI that falls off patent can be produced but fails to deliver revenue for generic companies.

So why such a low market penetration by generics for pyrimethanil?

- A number of mixture products have been introduced resulting in significant market segmentation and making it difficult for generic companies to take significant market share.
- Some of the mixture partner AIs are relatively old and no longer have patent protection, however, some mixture products have been granted patent protection based on synergistic activity and patents exist, which protect the market from generic competition.
- A relatively new mixture with fluopyram has been introduced, and fluopyram patents do not expire until 2023.
- Pyrimethanil gained inclusion on Annex I on June 1, 2007 with a data protection period which expired after five years thus keeping generics out of the EU market until 2012.
- Pyrimethanil is also used as a seed treatment and for post-harvest use on non-stored fruit, this is not a sector of the market that generics have traditionally been strong in.

Table 2
AI Patent Expiry vs. Data Protection Expiry

Active Ingredient	Expiry year for European Union patent for AI	Data protection expiry year
Benthiavalicarb	2015	2018
Cyflufenamid	2015	2020
Prothioconazole	2015	2018
Penthiopyrad	2016	2024
Fluoxastrobin	2017	2018
Penoxsulam	2017	2020
Spirotetramat	2017	2024

Source: Enigma Marketing Research, "What Happens to the Market After an Agrochemical Patent Expires"

Where Have All the Generics Gone?

There are many examples of when patent expiry occurred many years ago but no, or very little, generic competition has resulted. Spiroxamine provides a good example.

Spiroxamine is a systemic spiroketalamine fungicide discovered and developed by Bayer CropScience in 1987 for control of powdery mildew and other fungal diseases on cereals, bananas, grapes, hops, and ornamentals.

Spiroxamine is sold in most of the major markets in the world, and global sales of spiroxamine-based products reached $126 million in 2014. But with the generic sector having less than 5%, this has been a major success story for the post-patent defence strategies employed by Bayer. Some of this success can be attributed to:

- A number of mixture products have been introduced resulting in significant market segmentation and making it difficult for generic companies to take significant market share.
- Many of the mixture products contain prothioconazole and in the EU SPCs exist, for a two way mixture of prothioconazole and spiroxamine, with expiry dates in 2020 and with bixafen and prothioconazole with expiry dates beyond 2024.

Since the expiry of the basic spiroxamine patent in 2008, Meridian Agritech launched its spiroxamine product, Spiral, in South Africa. Other generic products have also been commercialized by several companies throughout spiroxamine's markets and Shaanxi Hengrun Chemical Industry Co., Ltd. has been identified as a manufacturer of spiroxamine, but to date market penetration is very limited.