Patent Focus

Researched and written by Genericsweb

Genericsweb is a provider of information products and services to the generic pharmaceutical industry. Its flagship product, Pipeline Patent Intelligence is the industry leader in providing comprehensive research and analysis of patents protecting pharmaceutical products worldwide.

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Use of patents in drug lifecycle management

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THE REASON FOR LIFECYCLE MANAGEMENT

Lifecycle management is a term often used by innovators when referring to the efforts they go to in attempting to obtain maximum returns from their investment in new drug discovery. Most innovator companies dedicate entire departments to managing this valuable process that, if successful, will improve both the annual size and the longevity of earnings from products containing a single active ingredient developed by the innovator. It is also argued by innovators that such activities are conducted to maximise the therapeutic value of the discovery for the ultimate benefit of the patient. Contrarily, many members of the generic medicines industry argue that such practices are anticompetitive and result in higher cost of healthcare to the patient and government bodies, labelling the practice Evergreening.

METHODS OF LIFECYCLE MANAGEMENT

The management of the drug lifecycle may involve a variety of strategies, which could include any or all of the following activities, among others:

- *Branding*: Building a reputation with healthcare professionals and patients to build confidence in the brand, thus improving acceptance and minimising the impact of generic competition upon entry. Such branding is difficult for generic competitors to overcome as marketing is not traditionally the nature of their business, and both trade mark and common-law legal protection is often available to the innovator. For example, Nurofen remains the leading brand of analgesic product containing Ibuprofen in many countries, despite its patent expiry in the 1970s, a position which generic competitors may never challenge.
- *Product support*: Certain products benefit from supplementary support services that are provided by the innovator companies, dependant on their product being dispensed. Such services may be difficult to imitate by generic competitors due to the large scale and deep resources of the innovators, yet are valued enough by the healthcare professional to warrant a premium. An example of such support is the provision of blood testing services for Clozapine products, which clearly is of benefit to the patient.
- *Trade relationships*: Healthcare professionals are often criticised for participation in the increasingly complex reward schemes and other benefits offered to them by innovator companies. These, however, form the basis of trade relationships which, built over the period of any monopoly, offer some protection against the impact of generic competition.
- *Manufacturing cost advantage*: Over time, manufacturing technology may be refined to improve efficiency and ultimately offer

a lower cost for manufacturing the active ingredient or formulation. These manufacturing efficiencies may allow for margins to be maintained on certain products even after any price decrease due to entry of generic competition and may be monopolised by appropriate patenting.

- *Product improvements*: Many products undergo improvements after initial discovery and/or registration due to regulatory requirements or market demands. These may relate to new dosage forms, release profiles or dosing regimens, said to improve the safety or efficacy profile over existing products, and of those products that generics may be able to offer upon active ingredient patent expiry, should patent protection be available.
- *Product line extensions*: As further research is conducted, additional routes of administration or indications form the basis of extensions to the original product line, or may indeed be launched as a separate product line with its own branding. Such extensions may or may not be emulated by generic competitors, dependant on the data exclusivity and patent protection afforded in the relevant territory.

THE IMPORTANCE OF PATENTS IN LIFECYCLE MANAGEMENT

Of the above lifecycle management strategies, the benefits of the latter three are significantly improved if patent protection is obtained to monopolise the result of the innovator's research and development efforts. Data exclusivity provisions seldom offer useful protection of research conducted to provide the basis for product improvements. Such strategies would therefore be too risky in terms of the financial return on the investment if reliant on data exclusivity alone. If obtainable, a patent monopoly is far more effective than simply preventing a third party from referencing data, as the data can be easily reproduced if found to be approvable, and the costs of challenging patents are very restrictive to many generic competitors.

Of course, most generic competitors are aware of the increasing amount of patent protection being applied for by innovators. This is a true reflection of the use of such strategies, based on the belief by innovators that there is a financial benefit in allocating significant resources to manage and implement lifecycle strategies. Unfortunately for the generic pharmaceutical industry, this increased realisation and corresponding activity by innovators has caught the patent authorities around the world off-guard. With examination resources pushed beyond their limits, many patents have been granted that appear to protect non-inventive improvements to products. This often has a compounding effect in setting a precedent for similar patent applications, which are also awarded protection and the patent landscape thus becomes more crowded with protection of seemingly frivolous improvements to the state of the art.

As we await a turnaround in patent examination quality from most major patent offices, regulatory authorities appear to have taken the lead in recognising that variations in the polymorphic form of the active ingredient, or the excipients used in its formulation are not critical to establishing essential similarity and have amended their policies accordingly. This has made the concept of circumventing patents much more viable to generic competitors, and often one that is preferable to an expensive, drawn out and risky patent challenge.

Based on my experience, for the majority of pharmaceutical products still under patent in major territories, there appears to be at least one patent-related obstacle laid down by the innovator that must either be challenged or circumvented to enable launch of an equivalent generic product. Although the number of patent challenges mounted by generic competitors to remove these obstacles is on the increase, a more strategic approach is being adopted by generic firms themselves

in filing for patents to protect their own research and development efforts aimed at circumventing the innovator patents. Unfortunately, the quality of such patents is often no better than that of the innovator patents they seek to circumvent, yet the quantity is much higher. Furthermore, such patent filings by generic competitors, due to their timing later in the lifecycle of the drug product, create even more uncertainty than those of the innovator as the applications often contain broadly drafted claims that remain unexamined at the time of development of the generic product. This means that such developments are often carried out and approval sought at risk, in the hope that certain patent applications will not be granted.

So it seems that, although the lifecycle management strategy of protecting improvements to products, their use and their manufacture results in patent protection for the innovator, the problem is significantly worsened by the response of generic competitors, to the extent that each and every one requires substantive patent information management practices and expertise in dealing with patent strategy.

TIMING OF R&D FOR LIFECYCLE MANAGEMENT

For many years I have monitored the patent filing trends in relation to particular drug products with great interest. I have previously demonstrated the change in patent filing trends over time but did not go into great detail as to why the timings of patent filings throughout the drug lifecycle are such.[1] Because the regulatory and patent legislation is different in each country, as are the marketing approval dates and any subsequent extension expiry, it is difficult to predict exactly what the timing of patent filings for a particular drug is actually based on. For the purposes of demonstration, however, I will discuss a possible approach to lifecycle management of a hypothetical drug by the innovator from a patent perspective, and the typical response by generic competitors.

A drug product for which the first patent was applied for in 1980 (discovery) would benefit from 20 years patent protection in Europe. This protection would be subject to a further extension of five years when the drug product was first approved in the EU, say 12 years after the patent application date, that is 1992. Any later patent protection obtained as a result of lifecycle management should not ordinarily benefit from any extension, thus any R&D efforts relating to molecular forms, processes, formulations or use within the first five years after discovery would expire prior to the Supplementary Protection Certificate (SPC) and offer no significant benefit to the innovator. This demonstrates an incentive for the innovator to wait for at least five years before implementing any R&D-based lifecycle management strategies. Such activity is made even more unattractive by the uncertainty of the drug candidate at this early stage. Hence in the first five years after discovery, very little patenting activity should be seen.

Five to ten years after discovery, the innovator may start to look for patentable improvements to the drug product as part of a lifecycle strategy. After five years, the prior art base would be low and broader patent claims to technology are more likely to be granted and/or more difficult to invalidate. The longer the innovator can delay these first-stage activities, or at least the patenting of the resulting innovations, the longer the protection it will gain after expiry of the molecule patent extension. Patenting activity in relation to molecular forms, processes, formulations and uses should start to increase during this period, and protection is likely to be broad in scope, giving up to five years additional monopoly to one or more product lines beyond the active ingredient patent expiry.

In years 10–12, as the drug product proceeds through the development pipeline and nears regulatory approval, patents will be filed relating to preferred salts, formulations and perhaps dosing regimens. As the state of the art is quite advanced at this stage, patent

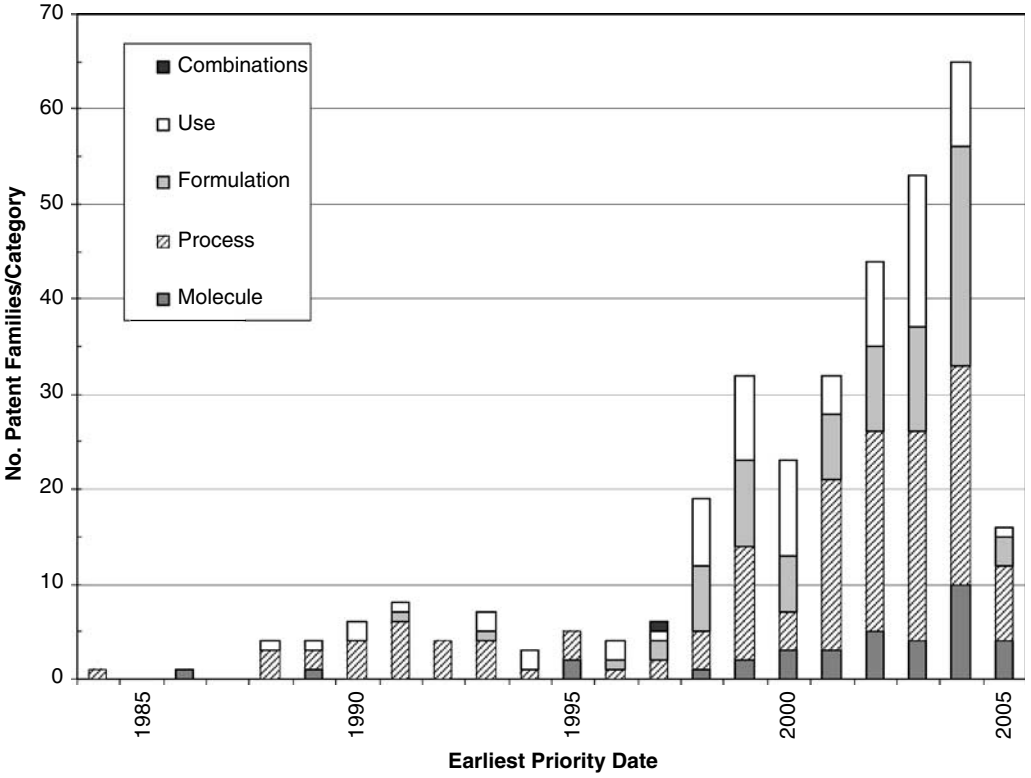

Figure 1: Patent filing trends — Atorvastatin.
Source: Genericsweb Pipeline Patent Intelligence

claims would be narrow and should be able to be circumvented by generic competitors, but occasionally broad patent filings are granted that represent significant obstacles and extend the uncontested life of one or more product lines by more than five years.

In the years immediately following launch of the innovator product (12–15), it meets the attention of more strategic generic competitors. These analyse the patent landscape and determine the best approach to launching a generic product as early as possible. They then file their own patents and block holes left by the competitors, seeking to secure as much of the generic market for themselves as possible. As more and more generic companies flag the drug as a potential project (years 15–20), an abundance of patents are filed protecting methods of circumventing the innovator patents, as well as those filed by generic competitors that have been published. The inherent 'blind spot' in patent systems around the world, however, means that a filed priority application is not published for 18 months and therefore massive amounts of overlap in patent claims occurs, causing significant wastage in the generics industry.

In years 20–25 the patenting activity by generic firms usually remains strong, but at this late stage there is very little uncontested technological ground remaining, so much of this activity is wasted. As generic competitors seek to finalise their product for registration and clear the way, many patent cases are brought to eliminate obstacle patents and many partnerships are formed with non-infringing suppliers of active pharmaceutical ingredient and finished product. Clearly, the corresponding abandonment of 'in-house' projects by less strategic generic players represents further wastage in the industry, which is a positive result for the innovator's lifecycle strategy.

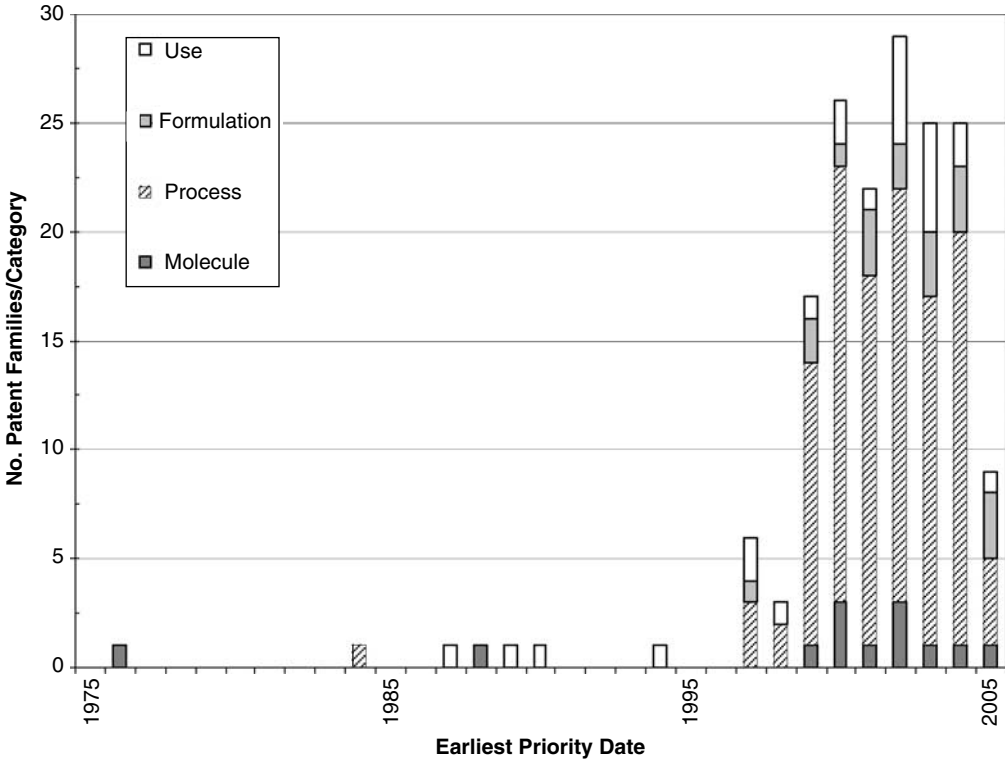

Figure 2: Patent filing trends — Citalopram.
Source: Genericsweb Pipeline Patent Intelligence

Finally, upon expiry of the active ingredient patent and its extension 25 years after discovery, a well-managed product would have limited generic or no competition for at least a few more years, with many generic competitors awaiting expiry of a later patent to launch their product.

Figure 1 shows the patent filing trends graph for Atorvastatin (patented 1986, launched 1996) as a good example of lifecycle management using patents, and the corresponding reaction by generics. We have already seen many patent actions with regard to this molecule. Although this does not exactly mirror the hypothetical example given above, it shows a very similar pattern.

Conversely, Figure 2 shows the patent filing trends in relation to Citalopram (patented 1976, launched 1989), generic versions of which were launched with ease by a multitude of generic competitors on the day of molecule patent expiry. The late surge in patent filings was predominantly due to a belated consideration of the effect of generic competition by Lundbeck, the innovator.

THE FUTURE OF PATENTS AS A LIFECYCLE MANAGEMENT TOOL

It is clear from the effect on the generics industry that patent-based lifecycle management strategies are an overwhelmingly successful tool used to protect the revenues of the innovators over the longer term. Unfortunately, the response by generic competitors in the high number and low quality of patent filings makes the situation worse for their industry, by injecting more confusion and cost into the development process.

There is no reason why innovators will not continue to pursue such strategies with a similar response from the generics industry. Over time, however, the patent examination

quality reforms being discussed by patent offices around the world will take effect and the quality and certainty of the breadth of patent claims will improve, reducing the effectiveness of such strategies. Meanwhile, there is a multitude of very low-quality granted patents that will cost one generics company or another a considerable amount of money to revoke or circumvent and this situation is likely to continue for another 10 or so years, while the low-quality patents work their way through the system to revocation or expiry.

Legislation is gradually being introduced in an attempt to recognise and reward innovator activities that are genuinely beneficial to the patient such as additional data exclusivity for new indications and additional SPC terms for paediatric indications in Europe. I, however, feel it is highly unlikely that this will stop the innovators from employing more self-interested strategies for preventing generic competition.

HOW TO MINIMISE THE EFFECT OF LIFECYCLE MANAGEMENT ON GENERIC DEVELOPMENT

Lifecycle management strategies have resulted in a complex and confusing patent landscape for nearly every unexpired drug product. In awaiting the surge of patent applications by generic competitors before reviewing the patent situation and considering a development strategy, the generic competitor often leaves its run too late. The more strategic generic companies are seeking comprehensive patent information as the first stage in the development process, and are doing so very early on in the innovator products life cycle. Thus they improve their chance of developing a non-infringing product, increase the chance of securing patent protection if they have circumvented innovator patents, and often have the opportunity of additional revenues by further licensing to slower-reacting generic competitors who need to 'buy-in' product. Simply looking at Orange Book or other basic patent information 5–10 years out from launch is no longer suitable practice; by that stage there will be a multitude of patents filed by generic competitors that will not be listed in the Orange Book, and which take a great deal of time and effort to search for and interpret, and may even take a further 18 months to be published. The way to minimise the effect of lifecycle management on generic developments is therefore simple: get comprehensive patent information, get it early and regularly update it.

Reference

1. Howard, L. (2007). Patent Focus: The changing face of patents in generic pharmaceutical development — Facts & figures. *Journal of Generic Medicines* **4**(2), 153–157.

