Patent Focus

Researched and written by Genericsweb

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

For further information please contact:
Leighton Howard
Genericsweb Pty Ltd
PO Box 20525
World Square NSW 2002
Australia
Email: l.howard@genericsweb.com

Genericsweb maintains its headquarters in Sydney, Australia and has regional offices in Slough, UK and New Jersey, USA.

Formulations patents in pharmaceutical development

Leighton Howard

is a patent information expert with extensive generics experience. He has worked within the professional patent information industry and major generic pharmaceutical firms and now provides consultancy services to the generics industry and government organisations via his company XIP Pty Ltd. He is also the founder of Genericsweb and remains instrumental in maintaining the high quality and accuracy of data contained in Pipeline Patent Intelligence.

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INTRODUCTION

One of my previous papers[1] discussed the patenting of molecular forms and the effect this may have on attempts to develop generic equivalents of pharmaceutical products. Another type of patent commonly seen in the pharmaceutical field is one that relates not to the active ingredient, but to the final dosage form in which it is contained, which is ultimately administered to the patient.

This paper will discuss the patenting of so-called 'formulation patents' and how they may affect those wishing to develop generic products where the reference or innovator product is protected by such patents beyond the life of the active ingredient *per se*.

WHY FORMULATION PATENTS ARE IMPORTANT

Formulation patents are an incredibly important aspect of lifecycle management from the perspective of the innovator, often blocking generic firms from competing with one or more of the dosage forms offered by the innovator until some time after molecule patent expiry. Where there is significant health or safety advantage in that particular protected dosage form over others in the product range and no generic equivalent is offered, such protection can be crucial in maintaining post-generic revenues, in particular when backed by a product switching strategy to increase acceptance of the protected dosage form. Conversely, where use of the protected dosage form offers no advantage in terms of the health or safety of the patient, the interests of cost minimisation by the prescriber or dispenser will result in limited benefit from such patenting as the cheaper alternative dosage form offered by a generic competitor will be dispensed.

Somewhere in between these two scenarios lies the most common one, where a generic competitor has developed a bioequivalent dosage form to one that is protected by a formulation patent, but has not infringed the formulation patent in doing so. The value of patent protecting the innovator formulation depends on acceptance of the equivalent generic dosage form by consumers and healthcare professionals. This, in turn, depends on a number of factors such as the type of active ingredient (eg appearance changes for antipsychotics), the age range of the predominant patient (eg flavours for children), ease of administration (eg insulin devices for diabetics), and even patient tolerance to inactive ingredients (eg lactose).

One further situation where formulation patents are important, albeit rarer, is where a generic competitor develops a dosage form that, in itself, is an addition to the innovator product line and offers advantage over the existing product. This may be an additional strength, a more storage stable formulation or a dosage form that increases patient compliance that somehow benefits from patent protection owned by the generic

competitor, or by a third party who has licensed it out. These types of generic products are often referred to as 'supergenerics'.

It is worth noting at this stage that Trade Marks and Registered Designs may also afford protection in regards to the appearance of pharmaceutical dosage forms that should be considered as a complete Intellectual Property review.

TYPES OF FORMULATION PATENT

Many readers of this journal will be familiar with the types of formulation patents that may be granted around the world; however, I am always surprised by the number of people who are not aware that simple incremental changes to a formulation over the prior art are patentable and represent a significant risk when attempting to develop a noninfringing generic. Below is a nonexhaustive list of formulation patent types that we regularly identify through our research.

Simple Recipe: Claims a list of the majority of the inactive ingredients found in a dosage form optionally combined with percentages or actual weights of each excipient. These patents are usually circumvented by changing one or more of the inactive ingredients or their weights, but caution should be exercised in countries where a 'doctrine of equivalents' applies.

Specified Inactive Ingredient: Possibly the cause of most frustration among generic developers, the identification of a small number of excipients, or a specific type of excipient, which is argued to have an unexpected effect in relation to the specific active ingredient, is often patented. This often raises the question as to how an excipient that has been used for decades can be patented in formulations containing a specific active ingredient.

Structure: Often solves instability or bioavailability problems in oral dosage forms using layers and heterogeneous phases. The Omeprazole formulation is perhaps the best-known case where the patented use of three phases prevented the enteric coating from degrading the acid-labile active ingredient, making development of alternate generic formulations very difficult.

Degradation Levels: Generally protects formulations that limit degradation and formation of impurities to certain ranges, where such degradation products may be harmful to the patient. These criteria may be protected in combination with a specific formulation or method, but may also be claimed independently.

Release Profile: Relates essentially to the rate and timing of release of the active ingredient, often in a way that blocks generic competition that needs to match the release profile of the reference product, thus infringing the patent. Occasionally, the 'invention' of a sustained-release product *per se* is sufficient to be patentable as seen in the case of Fluvastatin.

Sizes and Shapes: Physical attributes of the overall dosage form may be protected by the innovator, based on overcoming certain problems such as administration difficulties for larger tablets. Patents in relation to the size and oval shape of tablets covering multiple active ingredients, including Risedronic acid, have been granted by patent offices around the world.

Manufacturing Method: Certain active ingredients are susceptible to degradation or changes in their crystalline form (a problem that is becoming more prevalent given the increased patenting of polymorphs). The protection of certain methods of formulation of these active ingredients may therefore prevent generic competitors from using the reference product formulation, or possibly from formulating in a way that preserves the active ingredient sufficiently for regulatory approval.

Active Ingredient Strength: In certain cases, the strength of the dosage form *per se* has sufficient merit to be patentable. While the majority of these cases are protected in conjunction with a new indication or dosing regimen, a requirement for a new strength to

deliver the new indication or dosing regimen may be patented *per se*. An example of this is the 70 mg once per week tablet strength of Alendronic Acid, which received patent protection in many countries.

Device: Anti-asthmatic and insulin-type medications are segments that benefit significantly from device patents in terms of inhalation devices and injection pens, respectively. This is one of the areas where generics often add value over the innovator product, as demonstrated by Ivax who entered the market with a proprietary breath-actuated inhaler device containing a generic formulation of salbutamol.

TRENDS IN FILING OF FORMULATION PATENTS

So how did this current situation in regards to patenting of formulations arise? The relative number of formulations patents has decreased over recent times proportionate to the corresponding number of molecular form and process patents;[2] however, the absolute number of patent families filed still remains high. Figure 1 demonstrates that formulation patent filings in regard to Atorvastatin are dominated by generic manufacturers, all of whom filed patents after launch of the innovator product in 1996. Such patenting was in response to the small number of key formulation patents filed by Warner-Lambert prior to launch of the innovator product, but late enough in the drug lifecycle to extend beyond the life of patents protecting the active ingredient patent *per se*. This meant that generic manufacturers were forced to develop around the patents to gain earliest possible market entry and themselves have filed for protection of their solutions to the patent issues faced to prevent fellow generics from following suit. Please note that 'platform technology' patent filings are not included in the results shown in Figure 1, as such they are specific filings relating to the compound in question or its chemical or pharmaceutical group.

The result of this 'avalanche' of patent filings post launch is that many tiny incremental changes to formulations are sought to be protected by generic patent filings as many of the holes are plugged and ways around the patents are blocked.

The timing of these patent filings in itself creates a risk problem in terms of the uncertainty of the scope of any patent that is ultimately granted. Figure 2 shows the statuses of all European formulation patent applications relating to Atorvastatin at present. This demonstrates that at present, just over three years out from the expected generic launch date in Europe of 2011, around 70 per cent of the significant number of formulation patent filings for Atorvastatin are still undergoing prosecution

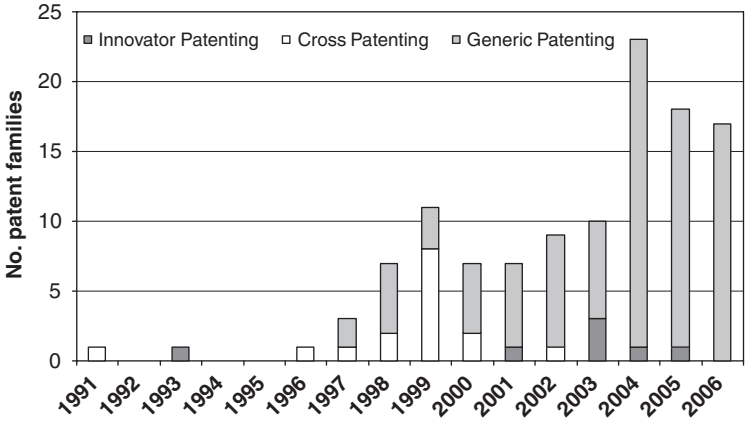

Figure 1: Timing and applicant type of formulation patent filings for Atorvastatin

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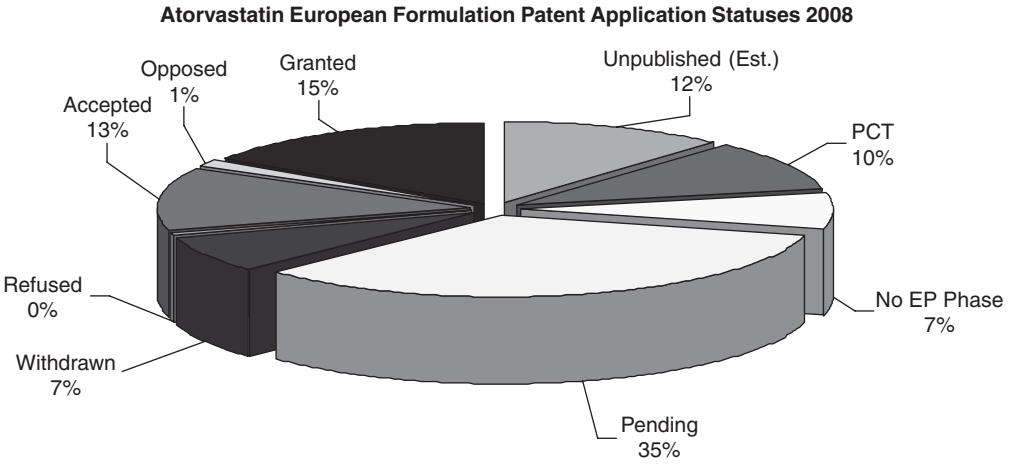

Figure 2: Statuses of European formulation patents for Atorvastatin — June 2008

and therefore have an undetermined scope of coverage.

The underlying assumption by scientists that commonly known excipients and dosage forms will not fall within the scope of patent protection is therefore false, especially when considering the risk associated with pending applications. This type of risk would be much smaller if the patent offices were to reliably examine patents to a certain level of quality, providing some certainty in the scope of any granted claims that an observer would expect. This will be discussed further in the next section.

THE FUTURE FOR FORMULATION PATENTS

In terms of the importance of formulation patents in the future, there appears to be a requirement for generic companies to develop new formulations to (a) circumvent existing formulation patents being granted to innovators and (b) to account for changes in stability and bioavailability of the active ingredient, where molecular form patenting requires that this is a different crystalline form or particle size. On this basis, the quality of patents being granted by patent offices around the world may be cited as a factor that will shape the future of formulation patents. The more innovator formulation (and molecular form) patents that are granted with seemingly insignificant incremental innovations over the prior art, the more generic firms are pushed to develop alternative formulations and protect their R&D investment by patenting these. The lack of certainty over the final outcome of these late-filed formulation patents due to varying patent quality within and across patent offices around the world is a significant problem from a generic developer's perspective and prevents true generic competition post active ingredient expiry.

According to European Patent Office (EPO) statistics presented in early 2008 (Table 1),[3] granted patents classified under A61K, the International Patent Classification code representing Preparations for Medical Use, were opposed on average over the past four years at a rate that is twice that of the EPO average for a given year. These data also show that one in ten patents granted by the EPO in the field of formulations are of questionable validity to the extent that an observer has sought to challenge the grant decision. When reviewing the results of such challenges, an average of 70 per cent of opposed patents in the field resulted in either revocation or amendment of the patent claims (Table 2), casting considerable doubt on the ability of the EPO to examine these patents with a high degree of quality in the first

Table 1: EPO opposed patents classified as 'preparations for medical use'

% Patents opposed	2003	2004	2005	2006
A61K	10.07	10.22	11.80	10.90
EPO Total	5.24	5.32	5.50	5.40

Table 2: EPO opposition decisions for patents classified as 'preparations for medical use'

A61K Decision %	2003	2004	2005	2006
Rejection opposition	23.6	24.5	15	28
Revocation	42.9	29.8	63	29
Maintenance in amended form	33.6	45.7	22	42

instance. According to the EPO, 40–50 per cent of patent opposition decisions in the 'Chemistry' field go on to Appeal, where it is thought that even higher opposition success rates would be achieved.

Unfortunately for the generic competitor the Opposition proceedings alone (without appeal) can last 27–35 months, during which time the poor quality patent is legally enforceable, representing a significant legal hurdle for the opponent when the patent is constraining generic competition. When presented with a more opponent-friendly system of pre-grant opposition at the recent EGA annual conference, Ingwer Koch, Director of the Patent Law Directorate at the EPO, agreed that this would be a positive step to address such issues, but said that it would be unlikely to be implemented 'in our lifetime'.

These are the results of analysis of one major patent office; however, I believe that similar quality problems exist in patent offices around the world where examiners routinely have a limited time to undertake substantive examination of a patent.

CONCLUSION

In summary, it is clear that formulation patents cannot be ignored in developing a generic pharmaceutical product due to the large amount of incremental patent filings witnessed for certain products. In fact, some formulation patents may be used to the advantage of generic entrants where they add significant value to the existing product line by use of truly innovative, patent protected formulation (or device) technology. The data presented in this paper, however, underscore the importance of reliance on consistently high patent quality to ensure that only true innovations are rewarded with patents to both innovator and generic applicants, so that generic competition can reduce risk and carry on with the business of developing low-cost, bioequivalent and fully substitutable products for the benefit of the patient and health funds. Needless to say, comprehensive patent searching and ongoing monitoring of pending patent applications and new publications are essential in managing the risk inherent in developing formulations for generic pharmaceutical products.

References and Note

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