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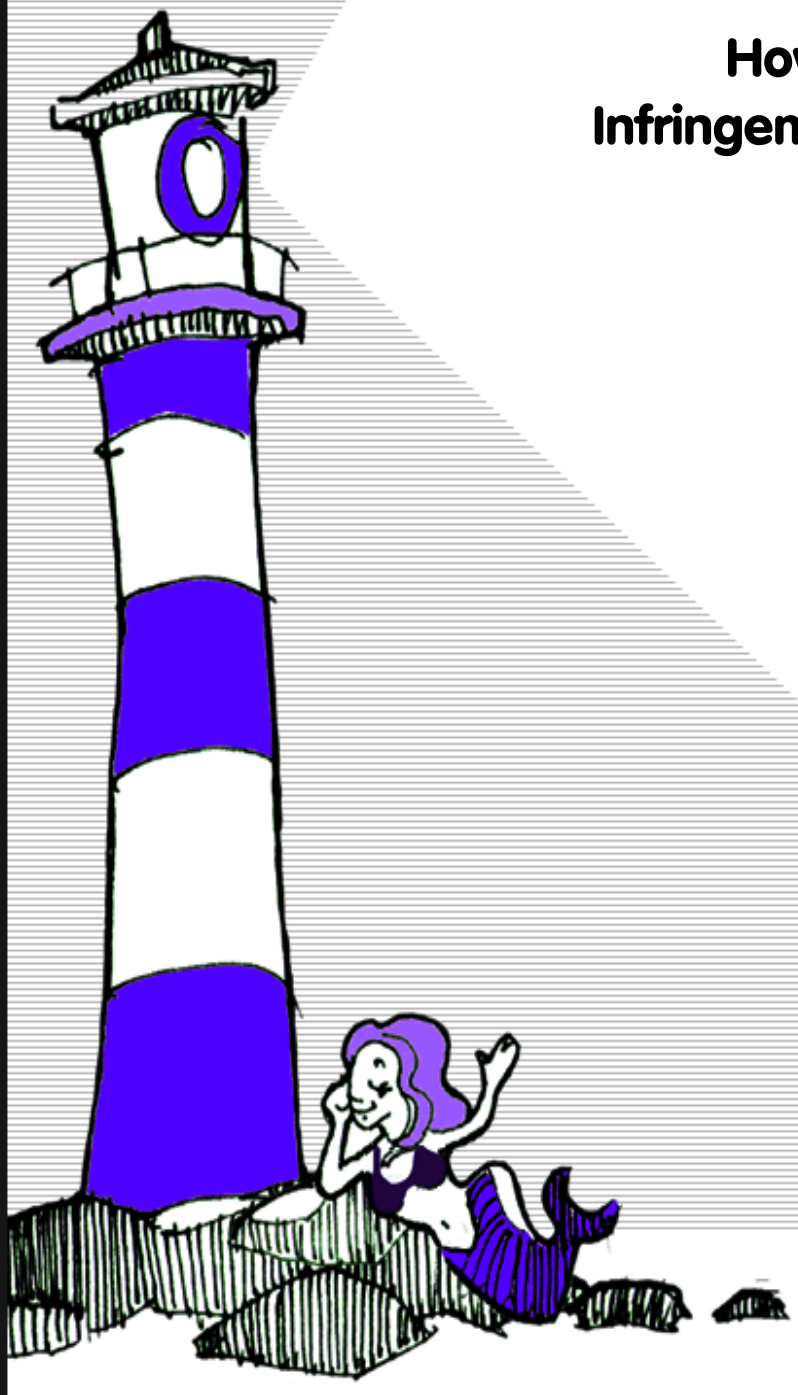
How to Avoid Patent Infringement in Developing APIs and Generics

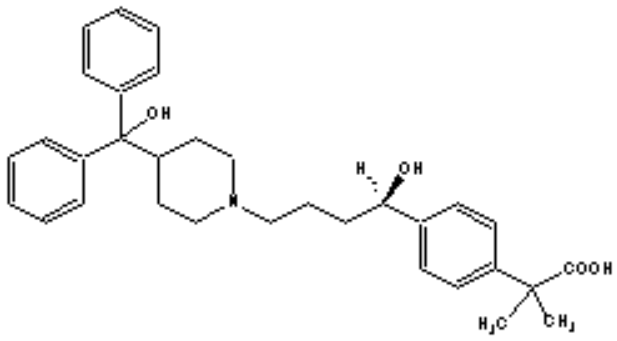


How to Avoid Patent Infringement in Developing APIs and Generics

Introduction

In developing generic pharmaceuticals for today's market there are many pitfalls, the most significant of which is infringement of patents. Based on the significant costs involved with litigation or the lost revenues from being forced to withdraw a product from the market, patent infringement is a potential threat not only to individual products, but also to any organisation without significant financial resources.

Drug originators are increasingly using intellectual property in an attempt to prolong the life of their branded products in the face of increasing acceptance, and even promotion of generics by government health authorities and a corresponding increase in the number of generics companies. As if this didn't make development of generics difficult enough, generics manufacturers are no longer content sharing the post patent-expiry market with other generics and are themselves using patents to block any development holes that the innovator has left open, in order to secure larger market share and cross-licensing revenues.



Where does this leave the small to medium-sized generics manufacturers, or those focused on the most cost-effective way of getting a bioequivalent, essentially similar generic onto the market? The answer is that they are in the middle of a patent minefield, where the location, size and type of each mine is constantly changing. This paper outlines some recommendations to overcome the threat that this situation poses to these generics manufacturers.

1) Understanding the Importance of Patent Information

In the past, generics manufacturers have usually had to wait until one patent expired – that protecting the active ingredient patent. In addition to the chemical compound per se, this patent would usually disclose at least one method of synthesis and any potential uses, as well as some formulations for its administration.

Although there is still a requirement for such disclosure in the active ingredient patent, innovator companies have taken advantage of the opportunity to patent almost any improvement to the basic information provided in the molecule patent, including: **polymorphic forms, salts, hydrates, reagents, reaction conditions, catalysts, purification methods, assay techniques, formulations, excipients, packaging, routes of administration, dosing regimen,** and new **medical use**.

Increased patenting in all technologies over the past decade has placed strains on patent offices around the world. The subsequent quality of examination, and therefore the patents granted across and within individual countries, is variable. As a result, it is no

longer acceptable to assume that a small modification to known technology is not the subject of a patent, as there is every chance that someone else in the world has considered it, and filed a corresponding patent application in your country.

Over the past 10-15 years, as many countries subscribed to the benefits of WTO accession and complied with TRIPS, both the type of protection offered by national patent legislation, and the term of the protection has changed significantly. In many countries supplementary patent terms or extensions are available, which adds further complexity to understanding when a patent is due to expire and what activities are allowed during the supplementary period. This has resulted in a confusing mixture of the type and length of protection in each country around the world.

This combination of changes to national and international legislation, and to the activities of both innovator and generic manufacturers means that each and every generics manufacturer, regardless of size or location must now be reliably and accurately informed of the patent position of a particular pharmaceutical product in order to reduce the risks associated with infringing third party intellectual property rights.

Table 1: Expiry data for an Atorvastatin molecule patent in selected countries

Country	Equivalent Patent Number	Status	Est. Expiry
AU	AU601981	s70 Extended	18/05/2012
CA	CA1268768	Granted	08/05/2007
DE	EP0247633	1768/92 (SPC) Extended	07/11/2011
GB	EP0247633	1768/92 (SPC) Extended	06/11/2011
US	US4681893	s156 Extended	24/09/2009 (PED)

Source: GenericsWeb Pipeline Selector Report, Atorvastatin

2) Obtaining Reliable, Accurate Patent Information

The first stage in determining the patent position is to conduct a patent search. Patent searching is complex, time consuming and very risky. It is a discipline that requires a unique skill set in order to reliably identify all of the necessary information and accurately assess its relevance to the generic drug development.

A patent search starts with one or more databases containing details of all published patents in the countries of interest across all technologies. Various figures are used to quantify the number of searchable patent publications, but let's assume a lower estimate of 50 million patents, for which various levels of searchable information across various publication dates is available. The next stage is to search the database to produce a subset of patents that contains all of the relevant publications in the country of interest over the time period of interest.

Because no one method of searching for patents is reliable, a combination of methods must be used, which may include the use of patent classification systems (from which you may select IPC, EPC, USPC or one of many others), applicant and inventor names, keywords and combinations thereof, structure and citation searching. Due to the large range of techniques used to minimise the risk of omission, a subset of 10,000+ patent publications is usually obtained.

The most reliable way of converting this subset of patents, which contains both irrelevant 'noise' and relevant patents, into useful information is to manually filter it.

This requires expert knowledge of the technical field i.e. chemistry/pharmacology, what constitutes a relevant patent and where to look for the necessary information in a patent document to determine relevance. As patent publications vary between countries, and each country may publish its patents in a different language, the searcher must also be capable of reading these foreign languages. The final requirement is time and patience – lots of it!

Obviously, this combined skill set is not common in the average employee of a generics manufacturer, thus outsourcing patent searching is often a cost-effective way of obtaining the information required in a reliable and accurate manner. However, caution should always be exercised to ensure that the actual searcher is suitably skilled in all of the above-mentioned areas.For larger organisations, an alternative could be to use an in-house patent searcher. As well as the initial, extensive costs of recruiting and training someone with a suitable skill set, ongoing commercial database fees, salary and training would be required in order to maintain suitable levels of reliability. However, such an employee could add further value by working from the known patent position towards a customised solution for the organisation rather than trying to integrate out-sourced information into the organisation's intellectual capital.

Without investing significant resources in either outsourced or in-house patent searching it is practically impossible for a company to identify all of the patents relating to a particular generic pharmaceutical product, resulting in increased exposure to patent infringement risk.

Table 2: Technical scope and bibliographic details for Atorvastatin patent

Pipeline Developer bibliographic detail - SI-1999-0000191	
Applicant:	LEK Lek Tovarna
Priority Numbers:	**Priority Dates:**
SI-1998-0000240 SI-1999-0000191	18/09/1998 06/08/1999
Class:	**Descriptions:**
Salts, Hydrates & Solvates	**1.** Di(alkyl)aminoalkane or alkylamine salts of statins.
Polymorphic Forms	**2.** Crystalline Pravastatin sodium in the form of colourless or pale yellow needles or radiating clusters, with a melting point of 170 to 174°C, prepared by dissolving Pravastatin sodium in a lower alcohol, adding ethyl acetate, cooling the mixture, and crystallising.

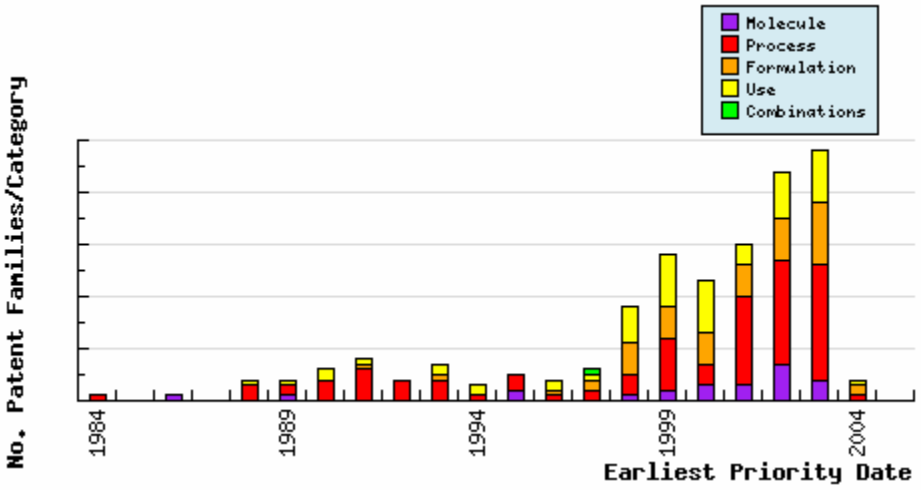
Source: GenericsWeb Pipeline Developer Report, Atorvastatin

3) Knowing When to Obtain Patent Information

Traditionally, a generic product would be developed and then a patent infringement search may be carried out as a final check prior to launch. Given the crowded and dynamic nature of the patent position in relation to a particular generic product today, this is a high-risk strategy.

Comparison of patenting in relation to older active ingredients compared with more recent ones shows that more patents are being filed earlier in the lifecycle, and by a larger number of interested parties. This is indicative of the nature of early patents filed by the innovator as well as the response by generics manufacturers who are forced to put significant R&D effort into circumventing them, and therefore seek some additional reward in licensing patents.

Figure 1: Atorvastatin Patent Filing Trends



Source: GenericsWeb Pipeline Selector Report, Atorvastatin

The key to developing non-infringing generics in today's industry is to obtain the information early in the process, preferably as soon as the active ingredient is identified as a development candidate. Early identification of key patents means that insurmountable patent problems can be accounted for in development schedules. Similarly, early recognition of patents that are hard to circumvent allows for allocation of suitable resources. Early development with respect to the patent position also offers further advantage if generics manufacturers choose to patent their own innovations, because the prior art base from which to establish novelty and inventive step is less advanced. This generally results in a higher patent application success rate and lower prosecution fees.

When negotiating contracts with customers, the question of the patent status is usually raised. If a supplier of generics has already obtained the necessary patent information, it not only provides the customer with confidence, but also expedites the negotiations. The most significant advantage is gained when the supplier has developed the product with every intended export market in mind and can confidently state that the product is non-infringing in that country. Such a statement will almost never be taken at face value by the potential customer, but will avoid the costly and embarrassing situation where the API or formulation needs redeveloping to avoid infringement in the customer's intended markets.

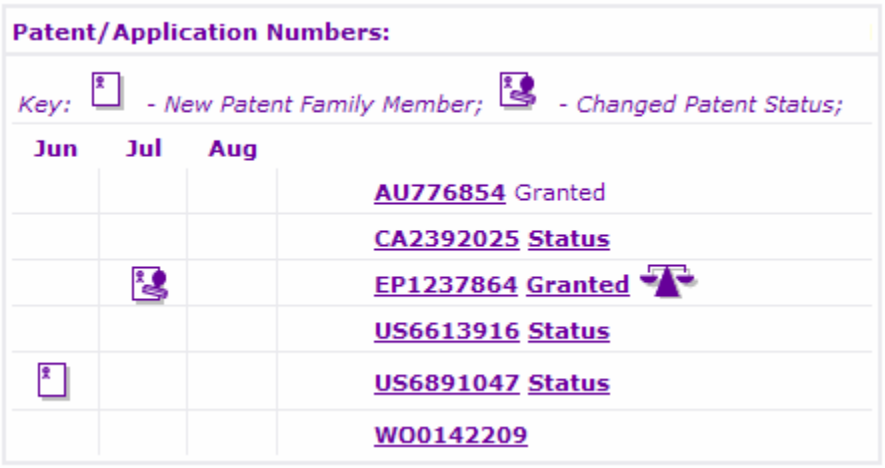
Not only is it important to obtain patent information early, but it is also important to

know the patent position for an active ingredient under development at any particular stage afterwards. The patent position is dynamic in nature and changes on a daily basis due to publication of new and equivalent patent applications, changes in procedural status and litigation. Given that an active ingredient may have more than 200 related patent families, each with 10 to 20 associated patent publications, keeping track of the patent position is no easy task.

It is also important to note that the patent system globally produces a 'blind spot' of around 18 months after filing a patent, before the full application is first published. This suggests that it is never possible to know the patent position at any one time; instead one must continually monitor the position to be alerted as soon as possible when a relevant patent application is published.

This task may be a significant challenge for the in-house patent searcher, however out-sourced patent monitoring services are available that employ automated alerting software or economies of scale to provide cost-effective solutions to this challenging task.

Table 3: Example of Update View for Atorvastatin Patent Family



Source: GenericsWeb Pipeline Developer Report, Atorvastatin

4) Understanding the Patent Position

Generic pharmaceuticals must generally meet the criteria of essential similarity and bioequivalence. From an economic and commercial perspective, they also need to be developed and manufactured over a low cost base. Patenting in relation to a particular generic product makes these criteria more difficult to meet, as different manufacturing or formulating options are protected.

Patents differ in significance, from surmountable 'Stumbling Blocks' through to major constraints or 'Brick Walls'. Many patents are applied for in the knowledge that they are not likely to be granted. These act as a deterrent to generics manufacturers who are not fully informed of the patent position and consider the patent to be enforceable. It is necessary to understand the significance of each patent identified and respond accordingly. This may vary from developing around the patented technology to seeking revocation, depending on the strategy and resources of the organisation.

Understanding the significance of a patent requires analysis of the geographical, technical and legal scope. Geographical or technical scope is relatively simple to ascertain by a technically qualified, patent

expert. Certain commercial products assist technical experts in understanding these elements. However, only legal experts who are qualified in the applicable country should interpret legal scope, as this requires knowledge of local legislation and case law, such as the doctrine of equivalents.

Finally, the understanding of the patent position needs to be shared throughout any part of the organisation on which it has an effect. This includes senior management, research and development and regulatory affairs functions, and even the manufacturing level, where slight changes to reaction conditions may change a non-infringing product to an infringing one. Such knowledge sharing is made possible by databases, which enable any member of the organisation to access up-to-date, relevant information regarding the patent position.

Centralised knowledge systems are being used by organisations in many industries to improve efficiency, maximise use of intellectual capacity and minimise the costs of obtaining duplicate information. The use of such systems to understand and disseminate knowledge regarding the patent position of a particular generic pharmaceutical is equally justified.

The costs of obtaining patent information through outsourcing or in-house capabilities have been discussed earlier, however the costs of not determining the patent position accurately to result in patent infringement are unquantifiable. On the one hand there are time-based costs of redevelopment, regulatory approval and re-building damaged relationships. On the other hand, there are financial costs in legal fees, waste product, legal fees and even damages. I will leave you with a quote from former president of Harvard Derek Bok, in response to a question regarding tuition fees:

"If you think education is expensive, try ignorance"

Written by Leighton Howard
27th September 2005
GenericsWeb

Leighton Howard is the founder of GenericsWeb a specialist provider of Patent Intelligence to the generic pharmaceutical industry. For further information on the range of products and services available please register you interest at www.genericsweb.com or send an email to l.howard@genericsweb.com

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