Patent Focus

Researched and written by Genericsweb

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Fluvastatin and Atorvastatin: A comparison of patent protection (Part 2)

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INTRODUCTION

Part 1 of this analysis, featured in the last issue of the *Journal of Generic Medicines*,[1] focussed on the so-called 'molecule patents' protecting the active ingredient *per se* of statin products Lescol (Fluvastatin) and Lipitor (Atorvastatin), and how different patent filing strategies could lead to significantly different strength and tenure of monopoly for the innovator.

This second part of the analysis will consider the effects of strategy and timing of lifecycle management activities that result in patenting of additional molecular forms, formulations and uses for these two products, and how this may add value to each product over their respective lifecycles.

The simplest way of summarising the extent of patent protection afforded by innovator lifecycle management is to look at patents that would be infringed if the innovator (Brand) product were to be copied in every detail by a generic manufacturer. This is by no means the only patent protection to consider, but provides the most appropriate place to begin analysis of the potential development problems likely to be faced in developing a generic equivalent for regulatory approval, and hence the presumed success of the innovator in protecting their monopoly.

It can be seen from the Tables 1a and b that patent families have been filed in relation to numerous aspects of the innovator product beyond the active ingredient itself. This protection will be addressed in terms of two types of patenting activity: product line extensions and product development.

PRODUCT LINE EXTENSIONS

It could be argued that individual active ingredients lend themselves to individual product characteristics such as route of administration, release profile and indications, and that it would be unfair to suggest that the variation between product offerings between two active ingredients is purely a result of the strategic elements of lifecycle management activities undertaken by the innovator. While I do not disagree with this position completely, my experience of evaluating patent protection of individual active ingredients suggests that certain innovator companies consistently obtain much better patent protection by launching a range of products containing their active ingredients and protecting each product line than their fellow innovator companies. Either these superior companies select active ingredients that are more likely to benefit from lifecycle management activities, or they are simply better at obtaining maximum protection for those that they do discover, the latter scenario being the most likely.

The Atorvastatin product line contains an immediate-release formulation for once-a-day administration and a combination with

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Table 1: (a) Atorvastatin key patents and (b) Fluvastatin key patents

Applicant	Priority application	Claims coverage
(*a*)		
Warner Lambert	US-1986-0868867 30/05/1986	Atorvastatin active ingredient — generic formula (racemate).
Warner Lambert	US-1989-0384187 21/07/1989	Atorvastatin active ingredient — specific formula (enantiomer) and hemicalcium salt thereof.
Sandoz	US-1991-0805667 12/12/1991	Formulation of a statin comprising an alkaline medium capable of imparting a pH of 8 or higher to an aqueous solution or dispersion of the composition.
Warner Lambert	US-1993-0005708 19/01/1993	Stable, oral formulation comprising Atorvastatin hemicalcium salt and a metal salt additive.
Warner Lambert	US-1995-0001452 17/07/1995	Crystalline Forms I, II and IV of Atorvastatin and hydrates.
Pfizer	EP-1998-0936587 11/08/1998	Combination of Atorvastatin and Amlodipine for treatment of hypertension and hyperlipidemia.
(*b*)		
Sandoz	US-1982-0443668 22/11/1982	Fluvastatin active ingredient.
Sandoz	US-1991-0805667 12/12/1991	Formulation of a statin comprising an alkaline medium capable of imparting a pH of 8 or higher to an aqueous solution or dispersion of the composition.
Astra (reassigned to Novartis)	SE-1996-0003667 08/10/1996	Pharmaceutical composition for sustained release comprising a water-soluble salt of Fluvastatin in a matrix formulation, or diffusion-controlled membrane coated formulation.
Novartis	US-2000-0549222 13/04/2000	Sustained-release tablet containing granules of <200 microns that comprise Fluvastatin and a hydroxypropyl methyl cellulose polymer.

Amlodipine (Caduet), whereas the Fluvastatin product line includes an immediate-release formulation and a sustained-release, once-a-day formulation. Regardless of how this variation in product line occurred, a sustained-release product that increases patient compliance and is favoured by doctors and patients alike is more likely to obtain a higher proportion of the sales within the product line than a combination product that is limited by the occurrence of the combined indications as well as the fixed ratio of active ingredients in the dosage form, that is, the percentage size of the subset of patients would usually be larger for the sustained-release product. Therefore, on the assumption that each may obtain patent protection that extends beyond the life of the single active ingredient patent, and all other things being equal, more benefit is obtained by the innovator in attempting to develop a sustained-release formulation than the combination product.

The question of the patentability of different types of product line extension then arises. Patentability is determined by different measures around the world, even though the principle of the patent monopoly is often the same. The result of this disparity means that patent protection for a single invention may be gained in a 'blocking' manner in some countries (where launch of a generic equivalent to the extension product is not possible while the patent is still in force) and is gained only in a 'disruptive' manner in others (where the patent may be circumvented to launch a generic equivalent to the extension product while the patent is still in force). You may be forgiven for assuming that there is little chance of a patentee gaining 'blocking' patent protection of a seemingly obvious combination of known compounds, or an even more obvious sustained-release version of a known product combination. If the patentee is very smart,

however, almost any type of product line extension could be protected in a blocking manner.

In the case of Fluvastatin, a patent is identified in Europe that relates quite broadly to matrix- or membrane-type sustained-release formulations. This patent is due to expire in 2017, a full nine years after expiry of Supplementary Protection Certificates (SPCs) on the active ingredient, and is considered 'blocking' in nature to any generic sustained-release competition. Despite having undergone the European Patent Office (EPO) opposition procedure, this patent is still considered to be valid (subject to appeal). Patent claims with similarly broad scope have been applied for in the US, but have not yet been approved. Novartis also has further European and US patent protection on their commercial formulation in terms of the combination of the active ingredient particle size and the specific excipients used. This is considered to be 'disruptive' patent protection in that it may be circumvented by generic competition in a manner that still yields a bioequivalent product, but is nevertheless considered by some to be worthwhile backup in case Novartis fail in their attempt to block this line extension completely (see discussion section below for further comment on this aspect).

In the case of Atorvastatin, Pfizer have so far been successful in protecting both a kit form and a combined dosage form with Amlodipine in Europe, the latter currently facing opposition. In the US, patent claims protecting only the combined dosage form have been granted, which are also being challenged by a generic competitor. Again, this patent protection is 'blocking' in nature until its expiry in 2018 and is susceptible to challenges by generic competitors but, unlike Novartis, Pfizer has not backed this protection up with more defensible 'disruptive' patents as a fallback position, instead they have opted to file multiple applications stemming from the same priority application in many jurisdictions to bolster the protection. The pros and cons of such a patent filing strategy have been discussed in Part 1 of this analysis.[1]

In terms of product line extensions, we can see that two companies have taken two entirely different approaches both in terms of the type of extension and the patent filing strategy. Both have, at least for now, managed to secure a much-extended monopoly period for at least a proportion of their product lines beyond active ingredient patent expiry. The best strategy is yet to be determined, as this is dependent on the strength of the patent protection and, the acid test, the dollar value of their product line that remains uncontested after active ingredient patent expiry.

PRODUCT DEVELOPMENTS

Once the active ingredient has been identified as a candidate for launch by an innovator company, the product must then be developed in a manner that makes it stable, functional and efficacious as a final product. Decisions must be made in relation to the basic product in terms of the most appropriate salt, crystalline form, excipients, structural form, dosing regimen indications etc. In order to protect the 'core' product from susceptibility to generic competition after API expiry, many of these incremental decisions form the basis of patent protection, most of which will not expire until long after this time.[2] These types of patents are mostly not 'blocking' in themselves, but simply create different degrees of difficulty for generic competitors in developing a bioequivalent product given the regulatory parameters that they must work within.

In the case of Fluvastatin there are two such patents, one that relates only to the specific particle size and excipient types in the sustained-release formulation (discussed above) and the other relating to pH stabilisation of the active ingredient in the formulation. This latter patent is likely to cause many generic competitors to attempt to innovate around it, with varying degrees of success. Surprisingly, this key formulation

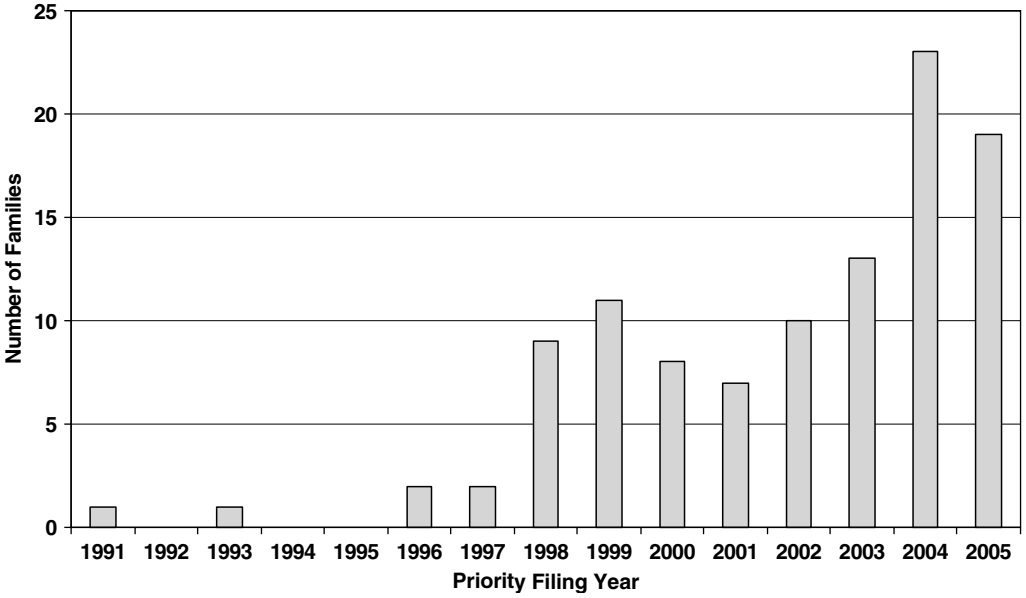

Figure 1: Statin formulation patent filings

patent for Fluvastatin is common to protection of Atorvastatin. The circumstances of this are unknown, but possibly resulted from some kind of licensing deal between Novartis and Pfizer. The patent is therefore likely to create similar formulation issues when developing non-infringing generic Atorvastatin products. Figure 1 demonstrates the increase of patent filings in relation to Fluvastatin and Atorvastatin as a response by generic competitors attempting to circumvent this pH formulation patent.

What Novartis has done differently to Warner-Lambert and Pfizer, is that it has made no attempt to protect the crystalline form of Fluvastatin in the commercial product whereas Warner-Lambert has introduced a clear barrier to generic competition in preventing them from using an identical Atorvastatin API. A quick look at the US DMF filings for Atorvastatin shows that many variations, including amorphous forms, different salts and different crystalline forms have been developed by generic competitors as an alternative form of the active ingredient. This has added to the headache of developing a generic Atorvastatin product, but will not prevent it beyond active ingredient expiry.

DISCUSSION

It can be clearly seen from the above analysis that different innovator companies choose to protect their products in different ways, sometimes led by the nature of the active ingredient but often led by lifecycle management activities including patenting in a 'blocking' or 'disruptive' manner. Two very similar molecules have been shown to result in entirely different length and extent of active ingredient protection, product line extensions and protection of different aspects of the commercial product. These differences could have significant effects in the financial returns on the brand product, and conversely the ease of development of a generic product by eager competitors.

Innovator companies argue that 'disruptive' patents are an essential part of minimising the scale of generic entry and protecting some of the market for the Brand product. Not surprisingly, I have a different view.

First, the increase in generic activity over the past few decades has resulted in these

'disruptive' innovator patents being circumvented by proactive generic developers who, in order to protect their investment in their own form of research and development, seek patent protection of their way around the innovator patent. With only a limited number of ways of circumventing a disruptive patent, the result is that it becomes flanked by generic competitor patents such that the mass of patent protection in relation to the product and any possible variant thereof is so large that any late-arriving generic player is essentially blocked by his/her 'early-bird' competitor. The net result of this is only a handful of generic competitors launching after active ingredient patent expiry, rather than a multitude, and a correspondingly higher price for the generic products. Surely, if the aim of the innovator company is to keep the generics industry at bay and maintain a relative upper hand financially, it would be far more beneficial to allow as many generic products as possible to launch at the same time, causing maximum price erosion upon patent expiry. This is based on the assumption that there is no price elasticity of demand in generic consumption once a certain generic price is reached.

Secondly, and most importantly, if a generic competitor intends to launch a product upon active ingredient patent expiry, regardless of whether they need to change the polymorphic form or the salt of the active ingredient, the route of synthesis and resulting impurity profile, formulation and excipients, even though the product is deemed approvable, it would no doubt be in the interests of patient compliance and safety to allow the generic company to copy the innovator formulation in exact detail.

In my view, the net result of 'disruptive' patents is therefore not only a stronger generics industry but also a series of generic products that may have passed the necessary regulatory tests, but are often different in some way, shape or form from the product that has been on the market for 14–15 years, and therefore unquestionably do not have the familiarity and track record of safety that is in the patient's best interests.

The same argument does not hold for 'blocking' patents which, if valid, protect a portion of the product line from generic entry completely and are a truly justifiable method of lifecycle management. Activities intended to switch patients from a non-patent-protected product to a protected line extension without considering the interests of the patient are, however, clearly not justified and should be disallowed where possible.

On a final note, although the message from patent offices around the world seems to be clear in terms of the questionable patentability of enantiomers, polymorphic forms, impurity levels, dosing regimens, release profiles and formulations using common excipients, there are many patents in force that have slipped through the net already, and with a good patent attorney, many more will slip through the net in the future. The short message is that the days of asking when 'the patent' expires are long gone, and such questions will nowadays be invariably met with a response of 'which patent?' and will for a long time in the future, especially for products developed by certain innovator companies.

Reference and Note

1. Howard, L. (2007). Fluvastatin and Atorvastatin: A comparison of patent protection (Part 1). *J Generic Med* **4**(4), 302–305.
2. The timing of life-cycle management activities was discussed in a previous article, Howard, L. (2007). Use of patents in drug lifecycle management. *J Generic Med* **4**(3), 230–236.

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