Patent Focus

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Fluvastatin and Atorvastatin: A comparison of patent protection (Part 1)

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Fluvastatin (Lescol, Novartis) and Atorvastatin (Lipitor, Pfizer) are similar products in many ways. They belong to the group of compounds labelled 'Statins', which is defined by their action in inhibiting the enzyme HMG CoA reductase, thus both are indicated for treatment of hyperlipidaemia and hypercholesterolaemia. Structurally, they share an enantiomerically pure dihydroxy pentanoate side group attached to a heterocycle, which itself is substituted by fluorophenyl and isopropyl groups, and both are marketed in the form of a mono-valent alkaline metal salt.

Despite these inherent similarities, there are, however, a number of differences between the ways in which each product has been protected in terms of patenting activity. Because the most significant factor affecting the style and extent of such lifecycle management activity of these products is the identity of the innovator, the aim of this two-part paper is to analyse the difference that this might make on the active pharmaceutical ingredient (API) patent expiry as well as the generic contestability of the product thereafter.

Novartis, the innovators of Fluvastatin, had a head-start over Pfizer's Atorvastatin of approximately 3½ years in terms of discovery and marketing authorisation (Table 1), both products taking a little under 11 years from the priority filing of the initial active ingredient patent to authorisation in a major territory. Generally speaking, European supplementary protection certificate (SPC) extensions allow for recuperation of 'time to market' of up to 11 years from the priority filing date of the API patent, after which the maximum five-year patent term extension is reached and valuable monopoly marketing time is lost by the innovator. It is interesting to note that approval times for both Fluvastatin and Atorvastatin are both slightly within this 11-year period, hence both products receive maximum monopoly marketing periods of 15 years from the date of first authorisation. As a result of legislation relating to SPC extensions, there is little incentive for the innovator to speed up the approval process for European markets, at least from a monopoly perspective, so more cynical observers might suggest that the timing of regulatory assessment for these products is not unintentional.

The US situation is, however, somewhat different, both in terms of normal patent terms and extensions thereto. US Patents filed on or after 8th June, 1995 have a patent term of 20 years from the date they are filed, whereas previously patents had a 17-year term from the date they were issued. As a transitional measure, all patents (other than design patents) that were in force on 8th June, 1995, or that issued on an application that was filed before 8th June, 1995 have

Table 1: Key dates for Fluvastatin and Atorvastatin

	Fluvastatin	Atorvastatin	Difference
Priority date of API patent	22/11/1982	30/05/1986	+3yrs 6mths
First major marketing auth.	23/08/1993 (UK)	07/11/1996 (UK)	+3yrs 2mths
Approximate time to market	10yrs 9mths	10yrs 6mths	−3mths
API patent expiry (UK)	22/08/2008	06/11/2011	+3yrs 2mths
API patent expiry (US)	11/04/2012	24/03/2010	−2yrs 1mth

Note: mths, months; yrs, years

a term that is the greater of the 20 years from the filing date or 17 years from the issue date. Furthermore, extensions available under 35 U.S.C. s156 may extend the patent by a maximum of five years, while allowing a maximum of 14 years marketing life.

This is often confusing to the most proficient patent experts and can result in some seemingly unfair advantages to certain patent applicants. In this situation, patent-filing strategies begin to make a difference as innovators attempt to patent incremental improvements to the active ingredient, such as specific compounds (as opposed to generic formulae), enantiomers and salts.

Given the later discovery of Atorvastatin in the US and the similar time to market compared with Fluvastatin, one could be forgiven for presuming that patents protecting Atorvastatin would expire after the corresponding Fluvastatin patents. The US patent 5,354,772 protecting metal salts of Fluvastatin (based on the API priority patent application), however, was filed in 1993 and ultimately issued in 1994, providing a maximum expiry date of 11th October, 2011. In short, this gave Novartis a monopoly on Fluvastatin in the US (at least over the metal salt) of nearly 18 years before the six-month paediatric patent term extension was applied. Extensions available under §35 U.S.C. s156 were therefore not applicable in this case. Meanwhile, Pfizer was allowed to extend US patent 4,681,893 (protecting the API molecule generically) in respect of Atorvastatin by approximately 3½ years, yet still only managed a monopoly period of under 13 years until, before the six-month paediatric extension was applied.

Instead of filing numerous continuations and divisionals of the original API patent application in the US as Novartis had done, Warner Lambert (the patentee at the time) chose to file a new priority patent application protecting metal salts of Atorvastatin, as well as specifically claiming the desired enantiomeric form *per se*. This resulted in the US and European patents with expiry dates in late 2010, seemingly offering little or no benefit to Warner Lambert above and beyond the protection afforded by the original API patents. Until, that is, an administrative error resulted in the recent revocation of '893, their original API patent was in the US. With the later enantiomer/salt patent remaining in force, it provided a safety net which meant that Pfizer did not lose its valuable Lipitor monopoly to awaiting generic competition. Although this revocation is still subject to appeal, it demonstrates the value in filing multiple patent families to bolster patent protection.

When analysing the patenting of even the most basic element of a drug product, the API itself, there are a multitude of filing strategies available to the patentee, each having their own risk and return. In the case of Fluvastatin, Novartis skilfully prosecuted their patents to obtain the higher return in extending the monopoly life of Lescol far beyond the expiry date offered by any patent term extension in its most valuable market. At the same time, they still had a more basic patent in the same family, US 4,739,073 having an earlier expiry, to fall back on. In filing a separate salt/enantiomer

patent for Atorvastatin, Warner Lambert, however, may have lost a significant opportunity to extend its monopoly in the biggest market by use of the transitional patent expiry rules in force in the US, and their enantiomer/salt patents had a later priority date and so were inherently weaker than the corresponding Fluvastatin salt patent. This has resulted in mixed fortunes for Pfizer with challenges to patents in both families in many jurisdictions testing their protection to the limits, the implicit and explicit costs of which are significant.

Although the learnings of this particular analysis are difficult to implement in hindsight, they are demonstrative of the incidental nature of patent-filing strategy having significant effects on the return of a drug development. Skilful patent prosecution, filing strategy and an element of luck are all instrumental in maximising the returns from a drug development, without necessarily knowing what benefit a particular course of action will take in the future.

Part II of this analysis will consider the effects of strategy and timing of 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.