PATENTWATCH

Plavix franchise in jeopardy

The threat of losing market exclusivity for the blockbuster antiplatelet drug Plavix (clopidrogel), has suddenly turned into a reality for its co-marketers Bristol-Myers Squibb (BMS) and Sanofi-Aventis. The two companies have filed for a preliminary injunction against Canadian generics firm Apotex after it decided to take its chances against losing the patent-infringement lawsuit surrounding the drug and began shipping generic clopidrogel to the US. The move follows the collapse of a 'reverse payment' agreement aimed at settling the lawsuit, which meant the case would go back to trial.

The wrangle began when Apotex filed an Abbreviated New Drug Application for its generic version of clopidrogel and challenged the validity of a composition of matter patent (US 4,847,265) for the drug. Apotex had argued that the '265 patent, which is due to expire in 2011, is invalid because it is anticipated by a prior patent (US 4,529,596, now expired) claiming both enantiomers of clopidrogel bisulphate. Moreover, because the '265 patent only covers the (+) enantiomer, Apotex maintains that its product does not infringe the patent anyway.

The three parties eventually reached an agreement, which was subject to regulatory approval by the Federal Trade Commission and the state attorney general, in which Apotex would delay marketing its generic in return for a minimum US$40-million payout from BMS and Sanofi-Aventis. However, after concerns were raised by the regulators about the deal, a revised settlement was proposed. BMS and Sanofi-Aventis agreed that if Apotex launched its generic and the '265 patent was subsequently held to be valid and enforceable, then the companies would waive the triple damages they are entitled to and instead would limit damages to 50% of Apotex's net sales, or 40% if they were to launch their own authorized generic. The two companies also agreed to give Apotex 5 days working notice before filing for an injunction to stop drug shipments.

The settlement effectively created a 5-day window for Apotex to sell its generic without legal restraint and with limited financial risk, during which time pharmacies could stock up on the cheaper generic alternative and continue selling it until their supplies run out.

But at the end of July 2006, when the state attorney general still refused to grant antitrust clearance for the deal, Apotex exercised its right not to pursue the settlement and announced its intention to ship its generic product immediately, seemingly confident that it will win the infringement case.

At the time of going to press a decision on whether to grant the injunction had not been made, but BMS and Sanofi-Aventis hope to halt shipping of the drug and to recall drug that has already been shipped. Meanwhile they have already taken the measure of dropping the price of the branded drug. The case is the latest in a crackdown by regulators on attempts by pharmaceutical companies to use pay-off agreements to delay the launch of generic competitors.

Edward Wawrzynczak

Pfizer struggle to protect Lipitor patents

Pfizer's attempts to keep generic versions of Lipitor (atorvastatin) at bay in the US markets were dealt a blow recently when the US Court of Appeals ruled that one of its key patents for the drug is invalid because of a technical defect. Generic competition could now begin in 2010, and potentially leave Pfizer out of pocket to the tune of several US$ billion in sales.

The dispute centres on two Pfizer patents covering Lipitor that are the subject of a patent-infringement suit against Ranbaxy Laboratories. In December 2005, a Delaware District Court ruled that Ranbaxy failed to prove that the patents — US4,681,893 and US5,273,995 — were invalid or unenforceable and found the generics firm guilty of infringement. However, on appeal, although the US Federal Circuit agreed with the district court's findings in the case of the '893 patent, which broadly covers atorvastatin, it found fault with the '995 patent, which relates to the calcium salt of atorvastatin.

The key issue is Pfizer's failure to comply with the US patent law specification for making a 'dependent claim', which essentially requires that such a claim must refer to a previous claim and must also specify a further limitation of the claimed subject matter. Pfizer's problem is that claim 6 of the '995 patent covers the 'hemicalcium salt of claim 2' but claim 2 only recites 'atorvastatin acid' and crucially omits mention of 'pharmaceutically acceptable salts' of atorvastatin acid, which are covered instead in claim 1. The appeals court argued that claim 6 could have been properly drafted either as dependent from claim 1 or in the form of an independent claim, but as written it failed to specify a further limitation of the subject matter because it fell completely outside the scope of claim 2.

The '995 patent protected Lipitor until June 2011. If Pfizer is unable to correct the drafting defect at the US PTO and the appeals court decision stands, then Lipitor's protection will run only until the expiry of the '893 patent in March 2010. The potential loss of 15 months of market exclusivity could prove highly damaging to Pfizer, which recorded global sales exceeding US$12 billion for Lipitor in 2005.

Edward Wawrzynczak

Barr and Shire settle on Adderall

Barr Pharmaceuticals and Shire Laboratories have finally reached a settlement over Adderall, a drug for attention-deficit–hyperactivity disorder (ADHD). The deal means that a generic version of the drug will reach the market 9 years earlier than previously thought.

Barr Laboratories, a subsidiary of Barr Pharmaceuticals, originally launched its generic version of the drug — a mixture of immediate-release amphetamine salts — back in February 2002, claiming that Shire's patents were invalid and unenforceable. After Shire sued Barr, a lengthy period of litigation ensued. Now, in one of three agreements made between the companies, Duramed Pharmaceuticals (another subsidiary of Barr Pharmaceuticals) has signed a product acquisition deal for Adderall that nets Shire US$63 million. Barr is also allowed to launch its generic version of the drug, Adderall XR, under a licensing deal that starts in April 2009, 9 years earlier than the last Shire patent is set to expire, or earlier if another company launches a generic version of the drug.

As part of the settlement, Barr accepts that Shire's patents are valid and enforceable and will pay the company royalties equal to a portion of the profits from sales of the generic. Sales for the branded drug were approximately US$40 million in the year ending June 2006.

Chairman and CEO of Barr Pharmaceuticals, Bruce L. Downey, said that the agreements enable a "pro-competitive and pro-consumer introduction" of the generic much earlier than would previously have been possible.

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Protease inhibitors

On page 785 of this issue, Boris Turk reviews the current status of drug development against proteases for a variety of diseases, and explains that an ideal protease inhibitor would be a highly potent and bioavailable small molecule. Continuing this theme, TABLE 1 below details patent applications filed in the past year for small-molecule protease inhibitors with therapeutic applications. Data kindly provided by Cora Sevilla at Thomson Scientific.

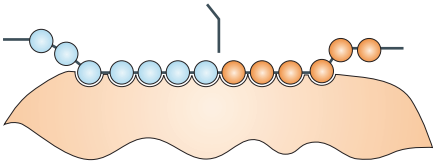

Table 1 | **Recent patent applications related to small-molecule protease inhibitors**

Patent number(s)	Assignee(s)	Subject
JP 2005053850	Teijin	A series of biphenyl amidine derivatives that act as airway-specific trypsin-like protease inhibitors; useful for prophylactic and/or therapeutic treatment of chronic airway disease and cancer.
WO 2006066693	Sanofi-Aventis	Novel cyclic urea compounds that act as metalloproteinase inhibitors with antiarthritic, osteopathic, anti-inflammatory and antibacterial properties among others.
WO 2006065590	XTL Biopharmaceuticals	Claims new pyridine and pyrimidine derivatives for use as hepatitis C virus protease inhibitors; useful for treating liver disease.
WO 2006065277	Pharmacopeia Drug Discovery & Schering Corp.	Heterocyclic compounds are claimed that inhibit aspartyl proteases; useful for cardiovascular diseases, and cognitive and neurodegenerative conditions such as Alzheimer's disease.
WO 2006061714	Pfizer	Claims novel ketone compounds that act as protease inhibitors; useful for treating severe acute respiratory syndrome (SARS) by preventing SARS-related coronovirus replication.
WO 2006056047	Merck Frosst	New amino-acid derivatives are described that act as cathepsin protease inhibitors; useful for treating osteoporosis, periodontal disease, tooth loss or bone fractures.
WO 2006060494	Axys Pharmaceuticals	Claims novel haloalkyl compounds that act as cysteine protease inhibitors and could be used to treat asthma, arthritis, multiple sclerosis, autoimmune diseases, diabetes, Alzheimer's disease and psoriasis.
WO 2006057152	Ono Pharmaceuticals	Covers an antidiabetic drug comprising a serine protease inhibitor; useful for preventing and treating diabetes and diabetes complications.
WO 2006060810	Axys Pharmaceuticals	A novel series of sulphonamide compounds that act as cysteine protease inhibitors; useful for treating autoimmune and arthritic diseases.
WO 20060122266	Coppi, A. & Sinnis, P.	A composition comprising a protease inhibitor, useful for preventing malaria infection by inhibiting sporozoite cell invasion, a stage at which the parasite does not multiply.
WO 2005113581	Schering Corp.	Claims novel substituted proline compounds that are hepatitis C virus non-structural serine protease inhibitors; useful for treating, preventing or ameliorating HIV and AIDS.
WO 2005085242	Schering Corp.	New ketoamide compounds useful for treating AIDS by inhibiting hepatitis C virus serine protease.
US 20050267102	Bayer Pharmaceuticals	Describes new substituted biaryl oxobutyric acids that act as matrix metalloproteinase inhibitors; useful for treating osteoarthritis, rheumatoid arthritis and periodontal disease and for slowing tumour metastasis.