

Current Patents Gazette

Patenting in Context

News & Highlights from week 0824

The UK Patent Journal (No 6212) this week reports the filing of a Supplementary Protection Certificate (SPC) application by **Merck & Co., Inc** for AIDS combination **Atripla** (efavirenz + **emtricitabine** + **tenofovir disoproxil fumarate**) on **EP0582455**, the product patent for efavirenz, as first reported by us two weeks ago in Current Patents Gazette 0822. Atripla, is now marketed mainly by **Gilead**, which pays royalties to **BMS** (and consequently Merck) for the efavirenz portion, originally owned by **Dupont Merck** which was subsequently acquired by BMS. Last week, Gilead announced that the USPTO had completed the second of four reexamination proceedings and confirmed the patentability of **US5922695**, which covers the composition of matter for tenofovir disoproxil fumarate. Previously, Gilead had announced that the USPTO had confirmed the patentability of **US6043230** following a challenge by the **Public Patent Foundation**. As worldwide sales of Atripla are expected to exceed \$3 billion in 2011, these decisions plus any granted SPCs are clearly very important for the partners.

The filing of two SPC applications by **Novartis** for the **Eucreas** combination of **vildagliptin + metformin** on **EP1741446** and **EP1137635** is also reported in this week's Patent Journal. As reported two weeks ago, only one SPC should be granted to a company for a single product, so it will be interesting to see

whether the use of slightly different company names is sufficient to circumvent this rule or whether Novartis will have to choose which patent will gain the SPC.

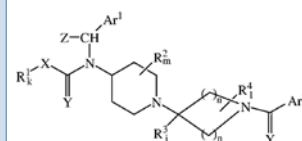
In another announcement, the Patents Journal reports the entry into force of an SPC on **EP0299602** for **GSK's ropinirole**. Originally discovered by **SmithKline & French**, in whose name this patent is filed, ropinirole is indicated for the treatment of Parkinson's disease and moderate-to-severe primary restless legs syndrome (RLS). The SPC entered into force on May 19, 2008 and is due to expire July 1, 2011. Interestingly, in light of the SPC applications mentioned above filed by Novartis, GSK already has an SPC in force for ropinirole on **EP0113964**, the Product case for ropinirole filed in the name of **SmithKline Beecham** (SKB) and which expires November 2008. Both SPCs were filed at the same time by SKB and as no previous certificate had been granted to the company for ropinirole and the patents were originally owned by different legal entities, the applications were deemed valid and both certificates granted with the consequence that the second SPC has entered into force just prior to the expiry of the first.

Last year we reported that **Merck & Co** had filed an SPC application on **EP1412357** for **Januvia** (**sitagliptin phosphate monohydrate**). This was unusual in that any

SPC granted would expire 15 years after the Marketing Authorisation which in this case was earlier than the patent expiry. At the time we postulated that Merck had filed the SPC application because of the new EU Pediatric Regulation which allows a 6 month extension to an SPC for appropriate pediatric studies. As the extra 6 months can only be added to an SPC (or application) and not to a patent, it appeared to us that the only way to get the extra 6 months in such cases, was to file an SPC application which would not previously have been granted, because it would have 0 length. It appears the UK IPO has taken this view also, as it has this week reported the grant of this SPC application with an expiry date of March 20, 2022 – although the patent does not expire until July 5, 2022. One question still remains. Will any 6 months pediatric extension expire September 2022, six months after the end of the "SPC" or December 2020, six months from the patent expiry date?

Worldwide sales for **sitagliptin** (**Januvia**) reported by Merck for 2007 were \$668 million and are predicted to approach \$2 billion in 2009 according to our Strategic Drug analysts.

Replidyne Inc has filed an initial UK application with claims to novel structures. The Colorado-based antibacterials specialist already has more than a dozen patent applications published, most recently focusing on methionyl tRNA synthase (MetRS) inhibition, including the case in which **REP-3123** is claimed (**WO2008039640**). It is possible that the present initial application continues the same theme, but it is unclear why it has been filed in the UK – the company's recent patents all claim US priority. Possibly there is a link with the collaboration with **GSK** that led to Replidyne licensing-in **bederocin** (**SB-682150/REP-8839**), now suspended (see **WO2004078119**, which does have joint Replidyne/GSK inventorship and was initiated in the UK).



Genzyme claims CCR5 modulators, indicating the continuation of a program initiated by AnorMED prior to its acquisition by Genzyme in 2006.

UK Initial Applications

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A0 applications filed May 5th – May 11th 2008 – expected to see publication in November 2009

• **Chroma Therapeutics** has filed a new application at the UK intellectual property office claiming inhibitors of Hsp90. This application was filed just before the publication of Chroma's **WO2008056120** on May 15, claiming a range of adenine derivatives as Hsp 90 inhibitors for the treatment of cancer, immune disorders and inflammation. No Hsp90 inhibitors have yet been reported in the company's pipeline but it is known that Hsp90 is one of the targets Chroma is investigating using its cellular accumulation "Esterase Sensitive Motif" (ESM) technology.

• **Glaxo Wellcome Manufacturing Pte** has applied for protection for novel compounds in the UK. On the face of it this is unremarkable, but this precise applicant name has so far appeared on only one previous patent publication, namely **WO2007109698**, an application relating to aerosol administration, filed jointly with **3M**. Although the name seems to imply a contribution from Singapore, that earlier application originated from inventors in Hertfordshire and Minnesota, and was filed by a GSK attorney based in North Carolina. There is evidence that the "Pte" name is being used in the context of other IP matters, including licensing agreements and litigation, but on patent applications its use does seem to be temporary and without any further significance – on the '698 case referred to above, for example, it has already been replaced by "Glaxo Group Limited" of Greenford on the official record.

• **Isis Innovation** has filed an initial UK patent application claiming small molecule inhibition of factor H binding. Because Isis is a technology transfer intermediary, it is impossible to say with certainty where this application originates, but it is clear that **Oxford University** is an established centre for fh-binding studies. In particular there is an MRC Immunochemistry Unit, in the Department of Biochemistry, from which numerous publications on the subject have emerged, most recently

in the context of *Neisseria meningitidis*. The history of the work now being carried out in Oxford can be traced back to academic work carried out during the 1990s, such as the **University of Leicester's WO9823638**. One of the key contributors to the field is Dr Anthony Day whose earliest work on binding of sugars to surfaces was patented by **Genencor (Danisco)**, but who then seems to have gone on to spin off **Plasso Technologies** from the **University of Sheffield** in order to exploit his findings in the form of diagnostic products.

• The **Medical Research Council (MRC)** has filed an initial UK application to protect compounds for use in stabilizing p53 mutants. Professor Sir Alan Fersht of **Cambridge University's** Department of Chemistry working with the MRC has been investigating p53 mutants and has published several papers and patent applications on the topic including an application entitled 'crystal structure of p53 mutants and their use' (**WO2008017863**) earlier in 2008. In an older PCT patent case (**WO03014144**), Friedler and Fersht disclosed molecules which can stabilize polypeptides including p53 mutants by binding to them at specific sites. They disclosed a 9 amino acid peptide (which they referred to as **CDB3**) which could stabilize p53 thereby preventing the generation of p53 mutants and so decreasing the occurrence of cell proliferation disorders. The current MRC application may be a continuation of this research.

• **Queen Mary & Westfield College** has filed an application for a biomarker for pancreatic cancer. The College has several ongoing research projects being carried out at the **Institute of Cancer** aimed at elucidating the functions of pancreatic cancer markers particularly S100P and AGR2 according to the university's website. This research is being conducted by Professor Nicholas Lemoine who is director of the Institute and Dr Tatjana Crnogorac-Jurcevic who is a senior

investigator. Their target is to find a minimal set of highly specific and sensitive biomarkers that will enable early detection of pancreatic cancer at the stage when curative surgery is still possible.

• **UCB Pharma** has filed a new UK initial application entitled 'Selection system'. The company has recently claimed methods for the selection of human acceptor framework regions for non-human (donor) antibodies and their use to produce humanized antibodies in **WO2008003931**. Antibodies created in this fashion may be used in the investigation of diagnostic and therapeutic agents. The earlier claims possibly relate to UCB's new Antibody to Hit Technology (A2Hit™), which the company uses to validate targets, specific sites on the target and specific contact atoms and their three dimensional positions in space. This increased knowledge of antibody-target structures enables the virtual screening of compound databases, selecting potential hits that may be assayed for function and identified as leads for further development. This new application may also be related to this program.

• The **University of Nottingham** has filed an application relating to cancer diagnostic **LIMD1**. Tyson Sharp, a lecturer in the Faculty of Medicine & Health Sciences, has previously published articles on LIMD1, for example, the role of LIM domains-containing protein 1 (LIMD1) in a tumor suppressor encoded at chromosome 3p21.3 which binds pRB and represses E2F-driven transcription (PNAS, Nov, 2004). He has also been awarded a grant to determine if LIMD1 is a marker for lung carcinogenesis. The current application appears to relate to the role of this gene in the diagnosis of cancer probably early stage lung cancer caused by tobacco.

• The **University of Surrey** has lodged an initial application in the UK for peptide manipulators of regulatory T cell activity. Although the university does not appear to

have previously filed applications on this theme, research is being carried out in the School of Biomedical and Molecular Sciences into regulatory T cells according to the university's website. Dr. Ernesto Oviedo-Orta, a lecturer in immunology, and his team have been investigating the role of regulatory T cells in the onset of arteriosclerosis particularly peptides derived from apoB-100 (the main protein component of oxLDL) which, they have found, can trigger regulatory T cells.

• The **University of Wales at Bangor** has filed two applications relating to an antifungal agent and fractionation of cashew nut shell liquid (CNSL), respectively. The applications are not necessarily related, but could well be, having been filed on the same day and given consecutive numbers. If so, the antifungal seems to be derived from the shell extract, which marks a complete departure from the work carried out at the university a decade earlier on particle board adhesive resins based on CNSL aldehydes. That previous application, **WO0031015**, was filed jointly with **Du Pont**, but in 2003 was transferred to **Cambridge Biopolymers Limited** of Duxford. In January 2004 the university's **Biocomposite Centre** was joint winner with Cambridge Biopolymers of a Sustainable Technology Initiative award. Given this background, the present invention could be a fungicide for use on wood, for example, rather than as a human therapeutic. However, CNSL does have a track record for yielding disease therapies, including the antihypertensive **anacardic acid** derivative described by **Diakron Pharmaceuticals** in **WO2004024513**, which act as T-type calcium channel blockers. Elsewhere, in India, histone acetyltransferase modulators from CNSL were shown to have anticancer properties in **WO2004053140**.