THOMSON

Current Patents Gazette

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Patenting in Context

DOLPHIN

The records appearing in this Gazette will be added to DOLPHIN, the database Of all pharmaceutical inventions in the next week. Based on the INPADOC database produced by the European Patent Office, it covers all national and international patents with relevance to pharmaceutical research and development published from 1968 onwards and selected patents from earlier years. DOLPHIN contains information on bibliographic data, contents, associated products, legal status, licensees and context of patents, which is presented in a format to convey all aspects of a patent at a glance.

News & Highlights from Week 0651

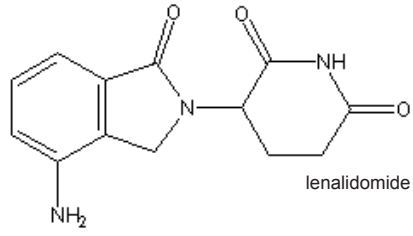
News that **Celegene** has purchased a plant in Switzerland from **Siegfried** serves to focus attention on the New Jersey-based company's **Revlimid** product, launched in January 2006 for myelodisplastic syndrome (MDS). The Swiss plant will be used to manufacture the active ingredient for this product, **lenalidomide**, an analog of **thalidomide**, which itself became a household word in the 1960s as a result of its **teratogenicity**. That history helps to explain some of the patenting which Celgene has been involved in by way of follow-up to its original claims to the NCE in **WO9803502**. The initial case was followed by a series concerned with the use of both lenalidomide and thalidomide, and in particular **WO0235440**, which with a cluster of Orange Book US patents contains claims to "Methods for delivering a drug to a patient while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug". In fact it was not until September 2003 that claims to a **polymorphic form** were filed (**WO2005023192**), followed a year later still by an improved **synthetic process (WO2006028964)**. This suggests that Celgene's principal concerns over lenalidomide during its early development were focused on its potential toxicity and effective administration rather than on its production. The Siegfried plant purchase now redresses that imbalance, and licensing of the drug administration patents to firms such as **Barr, Mylan, Roche and Ranbaxy** indicates that Celgene has enlisted substantial help in the commercialisation of lenalidomide.

"Disappointed" was **AstraZeneca's** perhaps rather understated reaction to the December 19th news that the European Patent Office had **rejected EP652872**, the case in which **esomeprazole magnesium** is claimed as a novel compound. The patent, which could have afforded strong protection for AZ's successful **Nexium** product until 2014, had been challenged by the German generics manufacturer **Ratiopharm**. There is another opposition in progress in relation to a relevant process patent, **EP773940**, and an oral hearing on that case is scheduled for March 7th 2007. Despite these problems, AZ points to other patents protecting Nexium, with expiry dates ranging from 2009 to 2019, and in addition there is **data exclusivity** effective in many European markets through to 2010. Esomeprazole held 28% of the global proton pump inhibitor antiulcer market in 2005, just ahead of **Altana's pantoprazole** and **Takeda's lansoprazole.** By 2010 however this share had been forecast to grow spectacularly to a dominant 58%, corresponding to annual sales approaching $8bn. It is likely that this performance will need to be revised downwards following the EPO decision, which also resulted in a fall of more than 4% in AZ's share price on the London market.

In its December bulletin, **Societa Italiana Brevetti (SIB)** reports that plans to create a single patent jurisdiction for all EU member states received a major setback recently. Currently, any granted European Patent comes under the jurisdiction of national courts for countries in which the patent is valid, making legal proceedings lengthy and expensive. The European Commission sought to obtain a mandate from EU member states to negotiate EU entry into the European Patent Litigation Agreement, establishing a single jurisdiction for patents granted under the European Patent Convention. However, Member States refused the mandate on December 4th which means the Commission will not be able to move forward without further consultations.

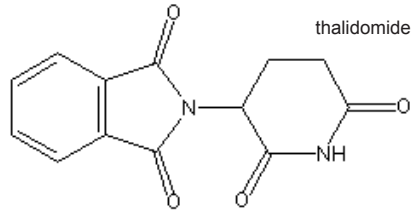
SIB also reported that the re-introduction of government fees for patents as well as maintenance fees in Italy seemed likely to go ahead early in 2007. The draft Financial Law containing this provision has been passed by the Lower House of Parliament and was being discussed in the Senate.

The PDJ (No 6135) reports the expiry of **Bristol-Myers Squibb's** SPC on **EP0053902** for **fosinopril + hydrochlorothiazide** (**Monopril HCT**) on November 26, 2006, further eroding the protection for fosinopril, which generated sales of $208 million for BMS in 2005. Most SPCs for fosinopril expired in July 2005 and companies such as Actavis were quick to launch generics, although SPCs are still active in France and Italy until late 2008. SPCs for the HCTZ combination generally expired at the same time as in the UK (November 2006).



lenalidomide

Celgene, who recently claimed a synthesis of lenalidomide in WO2006028964, has now purchased a plant in Switzerland from Siegfried AG, at which to produce the "new generation thalidomide".



thalidomide

UK initial ("A0") applications filed November 7th - 14th 2006

Addex Pharmaceuticals SA has filed four applications relating to novel compounds. The company focuses on the discovery and development of novel compounds for the treatment of major central nervous system (CNS) disorders including Alzheimer's disease, schizophrenia, anxiety, depression, pain and nicotine dependence. Addex has two mGluR5 negative allosteric modulators (**ADX-10059** and **ADX-48621**), a D1 selective antagonist (**ADX-10061**) and an mGluR5 positive allosteric modulator (**ADX-50938**) in clinical and pre-clinical stages of development. The company also has several discovery projects in advanced stages, including ADX1, ADX2 AD3 and ADX4.

Avaris AB, a biotechnology company founded in 2001 and based at the **Karolinska Institutet Stockholm**, has filed two applications entitled novel compositions and uses. The company develops and commercializes proprietary gene and cell therapy products in the field of chronic infections, cancer and inherited diseases. **DOLPHIN** has a recent publication from the company, **WO2006120439,** with the same title as these two new applications.

Barry Callebaut AG has filed an application entitled "compositions". **DOLPHIN** has two applications from the company, including **WO2006079731** which discloses the use of cacao polyphenols for treating prostate hyperplasia. The company is a world leading manufacturer of high-quality cocoa and chocolate products.

Biotica Technology Limited, has filed two applications covering novel compounds and method for their preparation. The company is focused on the discovery of **novel polyketide pharmaceuticals** through the targeted alteration of polyketide biosynthetic pathways. Its proprietary synthetic biology platforms enable both the specific and combinatorial biosynthesis of bioactive polyketides. Such pharmaceutical are potentially useful therapeutics for the treatment of cancer and other diseases.

Biovex Limited, has filed an application covering oncolytic viruses. The company is focused on the development of novel biologics for the treatment of cancer and infections disease. Its lead product for treating cancer is **OncoVEX $^{GM\text{-}CSF}$**. OncoVEX $^{GM\text{-}CSF}$ is in Phase II clinical development and is currently being tested in clinical trials for melanoma and head and neck cancer. **ImmunoVEX ^{HSV2}**, its lead product for prevention of infectious diseases, is a candidate vaccine for herpes simplex virus 2, the virus responsible for the symptoms of genital herpes. **ImmunoVEX ^{HSV2}** is in late stage pre-clinical development and is expected to begin clinical testing during 2007. **DOLPHIN** has eleven patents and patent applications from the company.

Dana Farber Cancer Institute now has an application on file concerning **the use of reversine and its analogs** in the treatment of cancer. Reversine is among the purine derivatives described by **The Scripps Research Institute** in **WO2005047524** as agents capable of **reversing stem cell differentiation**, although we noted there is confusion between the structure of reversine and the Markush structure claimed. This **dedifferentiation process** acts on mammalian cells which are committed to form muscle, turning them into **pluripotent stem-like precursor cells** capable of forming bone and cartilage, for example. These stem-like cells may be derived from mature tissue, thereby avoiding the technical and ethical problems associated with **embryonic stem cells**. The work seems to have been mainly confined until now to Scripps, whose earlier **WO2004093812** gave an indication of the direction in which this exciting research was moving. The Scripps work on cell de/differentiation has generally been patented jointly with **IRM LLC**, with the notable exception of **WO2005068437**, which names **Novartis** as joint applicant.

Hansa Medical AB has an application this week, claiming a method and kit. Previous applications by **Hansa** include **WO2006131347** (claiming the use of an IdeS polypeptide or polynucleotide for the treatment of autoimmune diseases), and **WO2004094468** and **WO2004074807** (both claiming methods for identifying anti-streptococcal agents).

Imperial Innovations Ltd is seeking protection for an application entitled **arginase**. **DOLPHIN** contains one prior application from this company: **WO2006015987**, claiming improvements in tourniquets.

Istituto di Ricerche di Biologia Molecolare P Angeletti SpA adds to its patent portfolio this week with an application claiming therapeutic agents. Recent therapeutic applications include **WO2006119975** (new thienopyrroles as HCV RNA polymerase inhibitors), **WO2006061638** (new heterocycles as HDAC inhibitors) and **WO2006046030** (new tetracyclic indoles as viral RNA polymerase inhibitors).

Kings College London has two applications this week, one claiming a method for monitoring cognitive ability or cognitive decline and the other a method for diagnosing or detecting **Alzheimer's disease**. A recent application from Kings, **WO2006003414**, claims a method for the prognoses or diagnoses of Alzheimer's disease by measuring GSK-3 levels.

Andrew J Langham has filed what appears to be his first application, claiming an AIDS and cancer cure and vaccine.

Optos PLC has filed what appears to be its first application appearing in **DOLPHIN**, claiming improvements in or relating to retinal scanning. This is likely to relate to the company's **optomap Retinal Examinations** technology, which facilitates the early detection of disorders and diseases evidenced in the retina.

Orion Diagnostics OY has an application this week, claiming sonication for reagent assays. A previous application, **WO2006119933**, claims a method of measuring the rate of analyte binding in immunoassays, using an initial step of ultrasonication.

Probiodrug AG has three consecutive new applications that all relate to various aspects of **glutaminyl cyclase inhibition**. Interest in this class of compound, also known as **QC inhibitors**, was first indicated in a filing program that began in May 2003, leading ultimately to the publication of five technically inter-related PCT applications, beginning with **WO2004098591**. The latter is interesting in that **OSI Prosidion** is now named as the assignee on a family member. In August 2005 Probiodrug reported a discovery program targeting **Alzheimer's Disease**, based on the effect of QC inhibitors on **amyloid plaque formation**. Rather strangely, the combination case **WO2005049027** skirts around the identity of the preferred QC inhibitor, concentrating instead on the second component, many examples of which are given. That could well indicate that a firm lead has not yet been selected, and the ongoing filing program that we are now seeing is a further argument for that viewpoint.

Scottish Biomedical Limited has filed a UK application titled **"Phosphodiesterase inhibitors"**. Based on their weak patent portfolio, it would seem to be a new area of research. However, their website suggests that they have extensive knowledge in that field and have been synthesizing novel phosphodieasterase (PDE) inhibitors for over 10 years. They are currently developing PDE 3 and 4 for potentially treating asthma. In November 2000, **Scottish Biomed** entered into a joint agreement with **Kyorin Pharma** to create and identify novel lead compounds in the field of allergy and immunology. Since then, Kyorin have made various filings involving PDE inhibitors, alone, or in combination with other drugs to treat CNS, cardiovascular, or allergic disorders.

Sosei R & D Ltd has made two applications this week. Namely: "**The treatment of inflammatory disorder and pain**" and the vaguely titled "**Novel salts and their therapeutic use**". Most of their recent filings relate to the use of inhibitors of T-cell proliferation and cytokine production to treat inflammatory disorders and pain (*eg see* **WO2006046007** or **WO2006027579**).

The **University of Exeter** and **Coventry Universit**y have filed for devices and methods for detecting **?-haematin** and **haemozoin**. This appears to be for developing hand-held non-invasive malaria detectors.

The **University of Manchester** has filed for the treatment of **gastrointestinal diseases**. The University has a gastrointestinal sciences research group, whose key activities concentrate on epithelial molecular physiology, the human brain-gut axis and population-based GI research, which is part of the Faculty of Medical and Human Sciences which is currently collaborating with **Salford Royal Hospitals NHS Trust**.

Peter Wilde has filed an initial UK application for the preparation of crystalline artemisinine, an anti-malarial agent, this week. This is likely to relate to the HFC134a solvent extraction technology previously applied to the extraction of flavours and fragrances from plants *see* **EP1200167**.

Xceleron Ltd, a York based company, is seeking protection for a library of compounds labelled with a radioisotope. This is likely to relate to the company's accelerator mass spectrometry (AMS) program for the indication of *in vivo* metabolism characteristics. This follows on from **WO2004077061** and **WO2006092584**.

7TM Pharma, a Danish group, has filed an initial UK application for cannabinoid receptor modulators. This appears to be the first patenting from 7TM in this area. 7TM has a **cannabinoid receptor 1** (CB-1) antagonists program for the treatment of obesity mediated through the peripheral nervous system. The program became part of the 7TM portfolio through the acquisition of **CareX AS** in May 2006.

Due for publication in May 2008