Product life-cycle management through second indications – a case study

This article explores the use of 'second indications' as a strategy and means of prolonging a product's life cycle while increasing a company's return on investment (ROI), using buprenorphine as a working example. Buprenorphine has been used as an analgesic for many years but is now assuming a critical role in the management of opioid dependence following its approval for this indication.

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Although world pharma sales reached a healthy $602 billion in 2005, growth remained below average at around 7%. Much of the sales growth during 2005 came from the developing markets, which have helped compensate flagging revenues in the developed countries due in major part to the loss of sales of older products to generic competition. The dearth of new products in the pipelines of major pharmaceutical companies will result in a slowdown of long-term sales growth. This remains a worrying factor and has encouraged companies to review their product ranges in search of new therapeutic indications.

The strategy of lining up approved products for second and even multiple indications is paying considerable dividends for companies such as Schering-Plough and Astellas.

Table 1: Products developed for multiple indications

Product	Comments
Thalidomide	Originally approved for morning sickness in pregnancy and removed from the market in the 1960s following side-effects of severe malformations in children born to mothers using the drug; thereafter licensed for leprosy as Thalomid (Celgene); both thalidomide and its analogues are also in development as anti-angiogenesis agents for cancer.
BCG	Originally a vaccine for TB; was approved for bladder cancer as Onco TICE/TICE BCG (Organon).
Acetazolamide	Under the brand name Diamox (Wyeth), it was originally a diuretic, which was subsequently licensed for epilepsy and is currently used for altitude sickness.
Aspirin	The first NSAID; now licensed (at a lower dose) as an anti-thrombotic.
Amitriptyline	Under the brand name Triptafen (Merck), is an antidepressant and was also licensed for neuropathic pain.
Methotrexate	Originally licensed for cancer under the brand name Ledertrexate (Wyeth); was licensed for psoriasis and as a DMARD for severe rheumatoid arthritis under the brand name Rheumatrex (Wyeth).
Gamolenic acid	Licensed for breast pain under the name Efamast (Pharmacia) and eczema as Epogram (Pharmacia).
Minoxidil	Launched as an antihypertensive under the name Loniten (Pharmacia) and later as Regaine, a topical formulation for male baldness.

A good example of this is buprenorphine, a drug that has been used as an analgesic for many years, but is now indicated additionally for the treatment of opioid dependence and detoxification of patients dependent on opioids, which include morphine, heroin and oxycodone (Oxycontin). The problem of opioid dependence is an increasing one in both the USA and Europe and buprenorphine is now assuming a critical role in its management.

Second and multiple indications

The strategy of lining up approved products for second and even multiple indications is paying considerable dividends, as witnessed by the approval of a number of key products for other indications. Recent examples include the approval of infliximab (Remicade; Schering-Plough), first approved for Crohn's disease and thereafter for rheumatoid arthritis, which subsequently became by far its major indication, and tacrolimus (Prograf, Protopic; Astellas) which was first approved for the management of organ transplant rejection and was later approved for the treatment of eczema. It is clear that companies are actively and successfully seeking multiple indications for all their products and achieving successes in product life-cycle management.[1]

In fact, around 50% of products currently in clinical trials for the treatment of autoimmune disorders are simultaneously investigated for several therapeutic indications, including rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease, within this group of diseases. For cancer, new and approved drugs are routinely investigated in the clinic for a wide range of different cancers; more recently, agents used for the treatment of leukaemias such as rituximab (Rituxan; Roche/Genentech) and imatinib (Gleevec; Novartis) are being routinely screened for disorders originating from the malfunction of the immune system.

Seeking indications for approved drugs has in fact been going on for many years but only recently has it focused on products approaching blockbuster status. Table 1 summarises examples of products that have found new life due to second indications.

This trend will continue to increase as new products are developed with mechanisms of action that are common to a range of disorders.

The case of buprenorphine, which we will illustrate below, shows how an old product can have new life breathed into it and how its successful management in a new indication has produced sales growth beyond all expectations.

Buprenorphine

Buprenorphine, a partial agonist at the μ-opioid receptor, was first discovered in 1966 and has been available as an analgesic for many years for the indication of moderate-to-severe pain, often accompanying cancer and other chronic painful conditions. It enjoyed modest annual market sales of approximately $45–50 million and was marketed in 45 countries. Patent protection of buprenorphine for most territories expired in the mid- to late 1980s. However, in two countries, the buprenorphine patent life had been extended by novel formulations – the suppository product form in Japan and the combination of buprenorphine with naloxone (1:1 ratio) in New Zealand (1995).

Although analgesic combinations of buprenorphine with either naloxone or naltrexone were patented in the mid- to late 1980s, the only country to accept a product registration was New Zealand; regulatory authorities in other countries were clearly concerned about approving an active ingredient, ie naloxone or naltrexone, which was of no benefit to the patient in need of pain relief. The presence of the naloxone or naltrexone was intended to deter product diversion leading to abuse or misuse of the product by opioid-dependent subjects.

The value created by the originator, Reckitt & Colman (now Reckitt Benckiser) consisted of an excellent registration dossier, high manufacturing quality standards and know-how, in addition to achievement of product registration in over 50 countries. Buprenorphine was identified as having potential for the treatment of opioid addiction as early as 1978. At this time, however, drug abuse treatment was not as politically and medically acceptable as it is today.

As a μ-opioid receptor partial agonist analgesic, the compound suffered from misconceptions and misinformation because of the wide acceptance of the mode of action of full agonist morphine and the misunderstanding of the attributes of a partial agonist as opposed to a full agonist. Two key benefits of buprenorphine compared to a full agonist are its reduced physiological problems during withdrawal and the 'ceiling' to its effects on respiratory rate, ie reduced potential to cause respiratory depression and limited maximal subjective effects. The latter property considerably reduces the potential for a patient to overdose when taking buprenorphine alone, and this attribute is of significant importance and benefit in the addiction treatment indication.

Path to treatment of drug abuse

The discovery of this drug's efficacy for this indication is a story in itself. The drug abuse treatment market provided 'orphan drug' status in the USA (with seven years' exclusivity) and market exclusivity in Europe (up to ten years). In addition, the combination of naltrexone and buprenorphine was also patent protected but not developed, although a naloxone combination has not been patented. Generic infringement on buprenorphine in analgesia had already been initiated.

Use of a second-indication strategy having marketing exclusivity and orphan drug status created a successful generic defence for buprenorphine; manufacturing know-how and unique product parity combining an analgesic effect with drug dependence treatment helped to convince the regulatory authorities of its added value.

In 1997, Reckitt Benckiser succeeded in obtaining Schering-Plough (S-P) as its world partner for international opioid dependence treatment, thanks to their early success in France. S-P had successfully worked with the French Medical Agency (FMA) to gain acceptance of an addiction treatment pharmacotherapy with a modified distribution channel, providing patients easier access to the products.

A major success occurred in the USA, with the amendment of the existing US legislation relating to opioid addiction treatment when the Drug Abuse Treatment Act 2000 was finally 'signed off' by the then President, Bill Clinton; this act now allows physicians to treat opioid-dependent patients in the privacy of their own offices, providing that the medication is based on a schedule III-V active ingredient. Buprenorphine is a schedule III drug substance and therefore can be used as an 'office-based treatment' therapy. Its major competitor, methadone, as a schedule II drug substance, is restricted solely to addiction clinics and so is subject to a much more limited distribution channel.

These changes in distribution channels and therapy availability generally have been successful in France and the USA, and it is evident that in other countries, addiction treatment products are becoming more available and more accessible to patients, with physicians being authorised to prescribe and administer the drug directly to their patients.

Over the last few years there has been an increasing acceptance that opioid dependence is a chronic, relapsing medical condition rather than a social and criminal justice issue.

Pharmacotherapy intervention is gaining wider acceptance, no doubt driven by concerns over the spread of blood-borne diseases such as HIV and HCV, which is linked to the sharing of needles by the addict community. The World Health Organization (WHO) now describes opioid dependence as a brain disease and has included both buprenorphine and methadone in its List of Essential Medications.

Use of a second-indication strategy having marketing exclusivity and orphan drug status created a successful generic defence for buprenorphine, even though 33 companies had been identified as either producers of the active substance or having a generic version of the analgesic. Manufacturing know-how and unique product parity combining an analgesic effect with drug dependence treatment helped to convince the regulatory authorities of its added value. To add to these salient features, a unique dossier, astute branding, similar dosage formulations incorporating a range of dose strengths and new formulations able to incorporate high doses of the drug, and realistic pricing, have all played an important role. A more transparent pricing scheme compared to the first indication was used as a means of obtaining governmental support and approval. Although the return on investment (ROI) is yet to be realised, it is believed that once peak sales in the USA are achieved, the ROI could become an industry record for a second indication product launch.

Table 2: History of buprenorphine

	First indication
Product form	Sublingual tablets, suppository and injectable.
Dosage	0.2–0.4 mg sublingual 3 times in 24 hours; 0.3 mg/ml intravenous every 4–6 hours.
Registration	Registered in > 50 countries and marketed in > 40.
Product sales	$45–50 million.
Patent and intellectual property (IP)	Original patents expired in the mid-1980s. Registration dossier difficult to imitate. High-quality manufacturing standards combined with specialised know-how. Patents on combinations with naloxone and naltrexone.
Generics	Denmark, Germany, Holland, India, Pakistan, Poland, Russia and Switzerland. Transdermal in EU now more widespread.
Marketing	Originator, licensing and distribution agreements.
	Second indication
Product form	Sublingual tablets (0.4, 2 and 8 mg strengths); also fixed-dose combination of buprenorphine with naloxone (4:1 ratio) tablets (contain 2 and 8 mg buprenorphine).
Dosage	Once a day administration; maximum daily dose 16–32 mg (country dependent).
Registration	Launched in France (1996) as buprenorphine-only product; in the USA, buprenorphine alone and combination product approved in October 2002; launched early 2003.
Product sales	Second quarter 2001 – $116m from France, Germany and UK. S-P reported $203m in 2006; $197m in 2005. Expected sales of > $500m by 2007.
Patent and intellectual property (IP)	7-year exclusivity – orphan drug status (USA). Up to 10 years' market exclusivity in Europe for buprenorphine alone from 1995. Patent on combination with naltrexone. Combination with naloxone gained EU approval through centralised procedure – 10 years' market exclusivity. All R&C unpublished data had to be repeated.
Generics	33 companies registered as producers of the active ingredient or with an analgesic indication and only one with a dependence indication.
Marketing	Originator and out-licensed to S-P.

History of buprenorphine

Table 2 summarises the history of development of buprenorphine as first (analgesic) and second (treatment of opioid dependence) indications.

The success of buprenorphine and other drugs developed for second indications should help assuage the current nervousness within the industry about the temporary shortcomings of the R&D pipelines, albeit on a lower level of sales than the highs of recent decades.

Note

1. Ansell, J. (2006) *Blockbusters are Alive and Well: Why Their Numbers Continue to Rise*. Waltham, MA: Decision Resources.

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