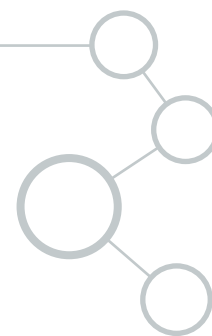


Vioxx: Lifting the Veil on the Dark Side of the Pharmaceutical Industry



By Catherine Pichereau, Senior Consultant at Bionest Partners



Catherine Pichereau is a Senior Consultant with Bionest Partners, an independent boutique offering consulting and advisory services for health care companies. Since joining Bionest Partners in January 2004, Catherine has been committed to the development of the financial advisory franchise. Catherine began her career in the corporate finance teams of Robertson Stephens (London, UK) and Bank of America Securities (London, UK), entirely dedicated to health care. She worked on M&A and private placement transactions for European companies, including biotechs, specialty pharma and medtechs. Catherine graduated from HEC business school (Paris, France) with additional qualifications from the Stockholm School of Economics (Stockholm, Sweden) and the Vienna University of Economics and Business Administration (Vienna, Austria).

On 30th September 2004, Merck voluntarily withdrew its \$2.5 billion COX-2 inhibitor Vioxx (rofecoxib) from the market. Strong evidence that the drug could be linked to severe cardiovascular adverse events left Merck with little choice. At the heart of the polemic, Dr David Graham, from the FDA's Office of Drug Safety, released the results of a study investigating the risk of Vioxx-related coronary disease. The study, involving 1.4 million Americans from 1999 to September 2004, showed that Vioxx-treated patients had a 34 per cent greater chance of developing coronary heart disease when compared with other drugs. In total, "an estimated 88,000-140,000 excess cases of serious coronary heart disease probably occurred in the US over the market life of Vioxx". Several analysts estimate Merck's potential liability could reach up to \$30 billion. Vioxx's sudden withdrawal has set a strong precedent in the pharmaceutical industry: several paradigms are starting to shift and new rules for success are progressively emerging.

First, questions are being raised on the sustainability of the traditional blockbuster model. Indeed, the need for longer-term safety data is likely to prompt regulatory authorities to re-visit the entire drug evaluation process, thereby impacting big pharma companies' corporate strategies. In particular, the pricing of future innovative treatments might have to be revised as pharmacoeconomic forecasts are bound to require a thorough assessment of possible safety concerns.

Also shaken is the belief that there is no room for late-comers in the pharmaceutical industry. Indeed, the Vioxx case shows that therapeutic alternatives should still be developed in markets where acceptable treatments are already available. Safety issues might affect class leaders as well as entire classes in the long run, thereby opening doors to the next available treatments. Last but not least is the unexpected recommendation from the FDA's Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to leave the other COX-2 inhibitors on the market, despite increasing evidence that cardiovascular risk might be a class effect. Is safety no longer the priority for industry regulators?

FIRST PARADIGM SHIFT: SAY ADIEU TO THE GOOD OLD BLOCKBUSTER BUSINESS MODEL

Vioxx is not the only drug to have been withdrawn from the market for safety reasons (see Figure 1): Propulsid (2000), Rezulin (2000) and Baycol (2001) were also pulled off the market after it was revealed they had caused multiple deaths. Since Vioxx had a particularly traumatic impact, health authorities are now in the process of implementing greater scrutiny in terms of long-term drug safety. The first example came at the end of 2004, when an FDA panel required Procter & Gamble to further study their testosterone patch Intrinsa for possible long-term safety risks. Such regulatory re-modelling will negatively impact development timelines and lead to increasing development costs.

In parallel, more stringent safety considerations might lead to declining target populations. Let's not forget that Vioxx was originally approved for the relief of acute pain, that is for short-term use. However, as a result of massive direct-to-consumer

advertising, Vioxx has been widely over-prescribed for long-term use in chronic pain, which resulted in cardiovascular adverse events. Strict use of Vioxx should have been enforced from the beginning in order to avoid such complications. It's too late for Vioxx, but actions can still be taken for the other COX-2 inhibitors. As the FDA suggested, their use should now be restricted: "patients who are at a high risk of GI bleeding, patients who have a history of intolerance to nonselective NSAIDs, or patients who are not doing well on nonselective NSAIDs may be appropriate candidates for COX-2 selective agents". Hence, market potential for COX-2 inhibitors is likely to be significantly reduced. Beyond COX-2 inhibitors, a large number of classes might be subject to such restrictions in the future, as an acceptable balance must always be achieved between efficacy and safety.

Additional pressure might also be placed on pharmaceutical companies with respect to pricing. Prior to its withdrawal, Vioxx cost \$1.2 a pill: four times more than diclofenac generic (30 cents a pill). Is this price difference legitimately accounted for? Recent events reveal the contrary. Consequently, it seems that the methods used to justify high pricing of innovative drugs might need to be re-assessed: pharmacoeconomic forecasts should factor in potentially related risks, including long-term safety. In a bleak scenario, pharmaceutical companies could be compelled to offer discounted prices for their innovative drugs, at least in their early marketing years, until full safety data has been secured. Thus, depending on future changes in pricing regulations, dollar sales of pharmaceuticals may well be under a lot more pressure than today. Higher development costs, lower volumes and pressure on pricing might turn the well-known blockbuster model into wishful thinking.

SECOND PARADIGM SHIFT: DON'T BE TOO DOGMATIC IN SELECTING DEVELOPMENT AREAS

Corticosteroids came to market in the late 1940s as one of the first effective therapies for inflammation. However, unacceptable dose-dependent side effects quickly outweighed their beneficial effects: osteopenia, bruising, weight gain and formation of cataracts or glaucoma. As a result, corticosteroids were progressively abandoned for the benefit of non-steroidal anti-inflammatory drugs (NSAIDs).

Nonselective NSAIDs, such as Voltarene (diclofenac, Novartis), Tylenol (acetaminophen, JNJ), and also naproxen, ibuprofen came to market in the 1960s. They work by blocking two enzymes (COX-1, which protects the stomach, and COX-2, which triggers pain and inflammation). Despite being efficacious, nonselective NSAIDs do cause significant side effects, especially when taken chronically and long-term. Gastro-intestinal bleeding is the most serious complication arising from such treatments. However, it can somehow be managed with the concomitant use of proton pump inhibitors.

In the late 1990s, a new class of pain relievers emerged: the COX-2 selective NSAIDs. The targeted approach of this therapy sounded highly promising indeed: similar efficacy to the nonselective NSAIDs and less – though not negligible – GI adverse events. Celebrex (celecoxib, Pfizer) was the first COX-2 inhibitor to be marketed (December 1998), and Vioxx was subsequently approved in May 1999. Both drugs witnessed the most rapid uptake of any class of drug: over \$1 billion in sales in less than 15 months on the market. Prior to Vioxx's withdrawal, both drugs were the market leaders (see Figure 2, page 37).

Despite prominent cardiologists, such as Cleveland Clinic Chief of Cardiovascular Medicine Dr Eric Topol, pointing out very early on the increasing cardiovascular risk of selective COX-2 inhibitors, these new treatments were seen as an attractive alternative to nonselective NSAIDs. What's more, with COX-2 inhibitors already on the market, the general consensus was that there was no room for the development of new therapies in this field. Today, not only are current treatment alternatives limited, but innovative late-stage pipeline products are also scarce. Assuming a big pharma had continued looking for better treatment alternatives in this segment and progressed a truly innovative compound to late-stage trials, they would now be first-in-line to reap significant dollar rewards. However, now that a thorough re-modelling is taking place in the segment, an opportunity has officially arisen – the race is on again.

Alternative treatments currently exist for moderate/severe inflammatory diseases, mainly TNF inhibitors. These biological agents, including Remicade (JNJ), Enbrel (Amgen) and Humira (Abbott), target TNF, a cytokine produced by T-cells and

Figure 1: Selected Drugs Withdrawn from the Market Due to Adverse Side Effects

Drug	Withdrawal Date	Annual Sales (\$m)	Reason
Vioxx	Sep 04	2,500	~ 60,000 deaths from cardiovascular adverse events
Baycol	Aug 01	900	31 deaths from rhabdomyolysis
Raplon	Mar 01	Small	5 deaths from bronchospasm
Propulsid	Mar 00	950	111 deaths from QTc prolongation
Rezulin	Mar 00	750	60 deaths from hepatotoxicity
Lotronex	Nov 00	Small	Bowel failure
Raxar	Nov 99	Small	Toxicity
Redux/Pondimin	Sep 97	380	Heart valve abnormalities

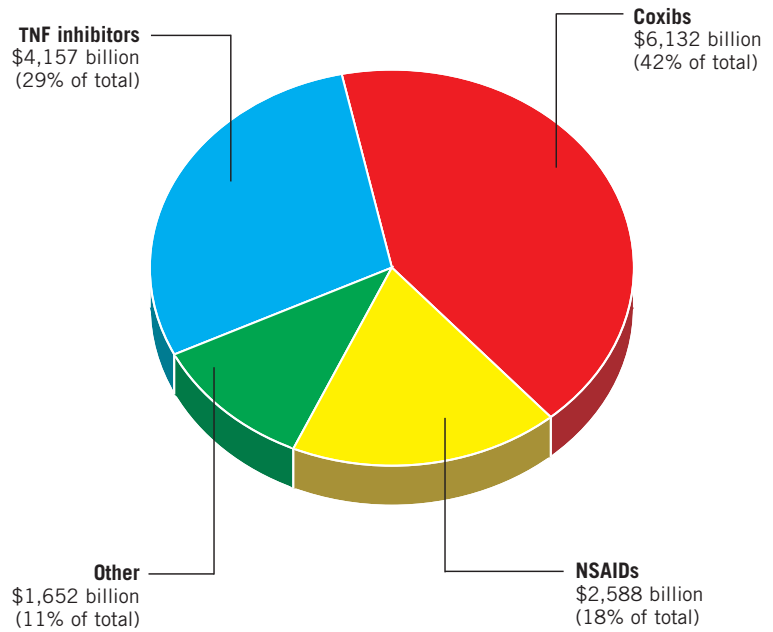
macrophages, and a keystone in the inflammatory cascade. These treatments have become the standard of care for the treatment of moderate/severe rheumatoid arthritis. However, issues such as cost and reimbursement, administration (IV) and long-term toxicity are preventing their front-line use. Physicians will likely reserve these treatments for the more severe cases of inflammation and for patients who have failed all other therapies. While still in early clinical stages, several innovative treatments are in development for mild/moderate inflammatory diseases.

Several next-generation COX-2 inhibitors are in late-stage development, such as Novartis' Prexige (lumiracoxib). Prexige has a higher selectivity for the COX-2 enzyme versus other currently marketed agents (700:1 selectivity for the COX-2 over the COX-1 receptor versus 250:1 for Vioxx, 30:1 for Celebrex, 7:1 for NSAID diclofenac and 1:1 for naproxen). Prexige also has no additional cardiovascular safety risk when compared to ibuprofen at one year. However, the compound has not been studied in a placebo-controlled trial of more than 18 months. Prexige is already approved in the UK, and a Mutual Recognition Procedure was filed in Europe in August 2004. NDA submission in the US is expected Q4:05 or Q1:06. Analysts also believe in GlaxoSmithKline's dual action 406 381, designed to treat both inflammatory and neuropathic pain. However, no long-term safety data has been gathered so far; GSK 406 381 is currently in Phase II.

Even more promising are two new classes of anti-inflammatory agents: anti-p38 MAP kinase inhibitors and TNF-alpha converting enzyme (TACE) inhibitors. These novel agents, orally available, are currently in Phase I and Phase II. The p38 MAP kinase is an intracellular enzyme that leads to production of TNF, IL-1 and COX-2. Inhibitors have the potential to be oral pills, which could be quite attractive. However, a number of companies have struggled to develop such compounds due to unacceptable toxicity in the liver. J&J/Scios have identified three orally available p38 kinase inhibitors, including SCIO-469 and SCIO-323: SCIO-469 has completed two Phase I trials and no serious adverse events were observed, even in patients who received doses of SCIO-469 significantly higher than the anticipated therapeutic range.

Vioxx was withdrawn five years after it came to market, although cardiovascular side effects had been somewhat suspected prior to approval. A first study performed in 1998 (Study '090') found that among 978 patients, serious cardiovascular events occurred six times more often in those taking Vioxx than those not taking Vioxx.

Figure 2: The \$14.5 Billion Anti-Inflammatory Market



Source: Analysts reports 2003

Phase IIa trials of SCIO-469 are complete but data has not been presented yet. J&J/Scios believe that SCIO-469 and SCIO-323 do not cross the blood/brain barrier and therefore CNS side effects should not be an issue. Two TACE inhibitors are also in development; Bristol-Myers Squibb is developing DPC-333, which completed Phase I. Preclinical studies demonstrated efficacy similar to Enbrel without an over immunosuppressive effect. Wyeth/Amgen is also developing TMI-005, currently in Phase I clinical trials, for the treatment of mild-moderate RA.

There is hope, but it still remains to be seen whether these pipeline products prove safe in the long-term.

THIRD PARADIGM SHIFT: COX-2 INHIBITORS ARE DEAD, LONG LIVE COX-2

Vioxx was withdrawn five years after it came to market, although cardiovascular side effects had been somewhat suspected prior to approval (see Figure 3, page 38). A first study performed in 1998 (Study '090') found that among 978 patients, serious cardiovascular events occurred six times more often in those taking Vioxx than those not taking Vioxx.

Figure 3: Timeline on Vioxx

Date	Vioxx Related Events
1998	Study '090' showing CV adverse events
Nov 1998	Vioxx NDA submission
May 1999	FDA Approval
Mar 2000	VIGOR study showing increased CV risk
2001	Vioxx labelling change
2002	Vioxx packaging change
Aug 2004	FDA approval to RA in children
Sep 2004	APPROVe study showing increased CV risk
Sep 2004	Vioxx withdrawn from market
2005	Vioxx re-introduced on the market?

However, Merck argued that the relatively small size of the study did not permit conclusions to be drawn.

A second study performed in 1999 (VIGOR study), enrolled 8,000 patients to confirm that Vioxx induced less GI side effects than other NSAIDs. In 2000, results showed that the patients under Vioxx had indeed less ulcers, but their probability of having a heart attack was five times greater. According to Dr Eric Topol, both studies constituted strong evidence that Vioxx was indeed unsafe. But it wasn't until the three-year APPROVe study, stopped early by a safety board in September 2004, that Merck decided to take action and withdraw the drug. The placebo-controlled study, which enrolled a total of 2,600 patients aged between 40 and 90, aimed to assess the recurrence of colon polyps as recorded by periodic colonoscopies. The primary safety endpoint was confirmed thrombotic events including stroke and myocardial infarction. Evidence of Vioxx's cardiovascular event was shown after 18 months of treatment: 1.9 per cent of patients on placebo had confirmed thrombotic events compared to 3.5 per cent on Vioxx.

In parallel to the Vioxx meltdown, tainting information has also been revealed on other COX-2 inhibitors, namely Celebrex and Bextra (valdecoxib, Pfizer). In 2000, the National Cancer Institute started the Adenoma Prevention with Celecoxib trial (APC) to evaluate Celebrex in colorectal cancer prevention. The study was halted in December 2004 because analysis by an independent Data Safety and Monitoring Board (DSMB) showed a 2.5-fold increased risk of major fatal and non-fatal cardiovascular events for patients taking 400mg of Celebrex a day versus those on a placebo. Even more worrying, increased cardiovascular risk was associated with 200mg, a recommended dose in Celebrex's label for rheumatoid arthritis. Similarly, multiple studies with Bextra showed an increase in cardiovascular events in patients undergoing heart bypass surgery. More recently, in February 2005, US private health insurance group Wellpoint announced alarming results of a comparative study performed in the US with 629,245 patients between January 2001 and June 2004: increase in

cardiovascular risk by 53 per cent with Bextra, 23 per cent with Vioxx and 19 per cent with Celebrex.

As was expected, a joint meeting between the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held by the FDA on 16th-18th February 2005 to determine whether these agents should be withdrawn from the market. While unanimous agreement was reached that all three COX-2 inhibitors "significantly increase the risk of cardiovascular events", the FDA committees decided against withdrawing Celebrex and Bextra. At this point, Merck was even considering re-introducing Vioxx on the market. Disturbing, isn't it? COX-2 inhibitors were approved for safety reasons: if they're not as safe as previously thought, why leave them on the market? Protecting public safety should be top of the agenda and it seems doubtful that the labelling change recommended by the committees (little black box warnings) will have a real beneficial impact on prescriptions. Did the 'smoking kills' warnings on cigarette packs substantially alter the habits of smokers? No. Rising prices did. In fact, COX-2 inhibitors should be withdrawn from the market until good evidence of safety has been secured. Meanwhile, compassionate use should be offered to those patients in strong need.

CONCLUSION

Merck screamed 'fire!' in the crowded pain market and panic quickly spread, affecting even nonselective NSAIDs: safety concerns have been raised for ibuprofen and diclofenac; preliminary analysis of the ADAPT trial, a long-term Alzheimer's disease prevention study with Celebrex and naproxen, also suggested that patients taking naproxen had a 50 per cent greater incidence of cardiovascular events compared to placebo. The NIH study was halted early in December 2004. Six months later, Constantine Lyketsos, a Johns Hopkins researcher on the steering committee for the ADAPT trial, declared that there was little basis for warning about cardiovascular effects of naproxen and that the ADAPT trial was stopped because participants would have been difficult to retain. The FDA committees rehabilitated the status of naproxen and lashed out at the NIH for halting the trial based on a perceived risk of cardiovascular events. Confusing... or is it?

The truth is, stakes are high. The judicial threat behind these growing allegations of safety concerns was probably starting to worry drug manufacturers as well as regulators. Vioxx already faces a hefty bill and if the NSAID fury was to continue, other big pharma companies could also get hurt. The FDA recommendation to keep COX-2 inhibitors on the market sends a clear message: the priority is to calm things down, not to ensure public safety... has the jury switched sides? ♦

*The author can be contacted at
catherine@bionest.com*