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# Sacrificing the cash cow

**In view of concerns about safety, could Amgen's aggressive promotion of erythropoietin (EPO) have jeopardized its billion-dollar franchise?**

Amgen must be longing for the days when the only worry for its EPO products, Epogen and Aranesp, was how to sell more drug to more patients. But now it looks as if it is going to fall foul of a familiar pharmaceutical malaise—overextension of its franchise. Just as off-label uses of Vioxx set Merck back over two years ago, so now misplaced enthusiasm about experimental uses of EPO threaten Amgen's blood-boosting franchise.

When it was launched in 1989, EPO was an orphan drug. But it came to dominate the US renal disease market, giving Amgen a virtual monopoly and tens of billion of dollars in revenue in the process. Epogen (EPO-α) is the most successful biotech drug in history. It is the biotech drug that launched a thousand companies by validating the concept that a biotech firm could commercialize a billion-dollar product.

By the end of the last century, EPO was used by almost every US dialysis patient. So Amgen, which already was selling the white-cell boosters, Neupogen and Neulasta, turned to oncology as a means of increasing EPO sales. The problem was that in the 1980s, Amgen licensed oncology uses of EPO to Johnson & Johnson. To compete, therefore, it developed Aranesp (darbopoetin-α), a hyperglycosylated version of EPO with longer serum half-life and higher relative potency.

After Aranesp was approved in 2001, Amgen undertook a massive marketing blitz, including direct-to-consumer television advertisements promoting the use of EPO in treating fatigue associated with chemotherapy.

But while the marketing machine was working very well—Aranesp is currently the sixth largest grossing drug in the world ($5 billion in global sales in 2006)—doubts began to emerge about the effectiveness and, indeed, the safety, of the drug itself.

In 2005, an independent study in the *Journal of Palliative Medicine* (**8**, 1144–1149) concluded, "Anemia is not one of the major contributors to fatigue in patients with cancer receiving palliative care." An editorial went further, stating "these data will help physicians resist the patient and family pressure to use erythropoietin because they saw it on television…. Erythropoietin is ineffective in relieving fatigue if anemia is not the cause. It is an expensive placebo."

At the same time, serious toxicity and potential cancer-promoting concerns have surfaced (see p. 373). In 2003, *Lancet* (**362**, 1255–1260) published clinical work that showed EPO had adverse effects on survival of patients with head and neck cancer undergoing radiotherapy. In the same year, Johnson & Johnson stopped its Breast Cancer Erythropoietin Trial (BEST) in nonanemic patients early because mortality among EPO-treated patients was higher than those on placebo. Last November, a study published in *The New England Journal of Medicine* (**355**, 2085–2098) showed that chronic kidney disease patients treated with high doses of EPO were more likely to have heart problems or to die. In January, Amgen announced that patients with cancer-associated anemia receiving Aranesp were found more likely to die than those on placebo. The following month, *The Journal of Clinical Oncology* (**25**, 1027–1032, 2007) reported a small Canadian trial in lung cancer patients that had been stopped early because those getting EPO were dying sooner. Shortly after this news broke, Hoffmann-La Roche suspended patient enrollment in a lung cancer trial comparing its new EPO (Mircera) against Aranesp because of a larger than expected number of deaths. The same month, the *Cancer Letter*, an influential Washington newsletter, reported that a head and neck cancer study in Denmark had been stopped last year because the cancer seemed to recur more often in patients being treated with Aranesp. As CEO Kevin Sharer conceded recently to investors, Amgen was aware of those results, but chose not to share them with the public. The Securities and Exchange Commission has now launched an investigation.

Perhaps inevitably after this calamitous catalog of clinical evidence, the US Food and Drug Administration (FDA) issued a 'black box' warning on March 9 for the labels of all EPO drugs, encouraging doctors to use the lowest dose needed to avoid blood transfusions.

Amgen does not come out of this well. Although seeking new indications for existing medicines is clearly a valid strategy, the company appears to have miscalculated the balance between expansion and the risks to its existing business—and potentially opened itself to charges that it has recklessly endangered patients' lives.

Tactically, the use of direct-to-consumer advertising for Aranesp, in the absence of solid clinical evidence, may not have been wise. Doctors did respond initially to the patient pressure that was created—this much is clear from the EPOs' sales figures. But the consequence of raised awareness of Epogen and Aranesp will mean that the backlash is more public, and more damaging, too.

Furthermore, Amgen has surely miscalculated strategically. Any benefits from the commercial push to extend Aranesp into new oncology markets are likely to bring relatively modest returns—Aranesp's 2006 sales in cancer-associated anemia, for example, were ~$500 million. But the repercussions of failure will be felt not only in cancer but also potentially across all EPO markets. A proportion of the whole $7.1 billion Epogen and Aranesp franchise—nearly 50% of Amgen's total revenue in 2006—is thus under threat.

Already, one Medicare administrator has announced it will no longer reimburse Aranesp off-label. US legislators have raised concerns that Medicare's payment system may encourage overuse of EPO, endangering patients' lives and wasting taxpayers' money. And when the FDA's Oncologic Drugs Advisory Committee meets next month, it may recommend even more restrictive labeling revisions. It is now up to Amgen to allay concerns over its EPO marketing practices. A first step would be to convince patients, physicians and legislators that it has not let corporate motives trump its responsibility to do no harm.