

The art of mismanagement

Is it possible that ImClone didn't do its homework on Erbitux's patents?


Sam Waksal's ImClone was not a company renowned for its business acumen. New management is not faring much better—at least if you believe major shareholder Carl Icahn, whose recent public rant about ImClone's incompetency led last month to the resignation of chairman David Kies and fellow shareholder William Crouse. Icahn ultimately has managed to oust the interim CEO and become chairman himself. In the midst of all this, the company has made it clear it is for sale, but has struggled to find a suitable buyer.

And now it turns out, according to New York District Court Judge Naomi Reice Buchwald, that ImClone has failed to consolidate the intellectual property (IP) covering Erbitux. On September 18, she decided that ownership of the '866 patent—which covers a method of inhibiting the growth of human cancer cells by administering monoclonal antibodies (mAbs) targeted at the epidermal growth factor receptor (EGFR) in combination with chemotherapy—belongs not to ImClone but to Yeda Research and Development, the commercial arm of the Weizmann Institute.

ImClone may actually have been ingeniously 'strategic' in its use of others' IP. Indeed, doubts have lingered for some time about the inventorship of the so-called '866 patent that covers Erbitux. In its original prosecution of the patent, for instance, the US Patent and Trademark Office (USPTO) noted with surprise that Weizmann scientists were authors of a relevant, if not central, scientific publication but were not named on the original patent application.

Then in 2000—14 months before the patent issued—Yeda discovered the existence of the '866 patent citing large amounts of the Weizmann work. Weizmann sued ImClone two years later. Finally, when ImClone exclusively licensed the technology, it agreed to prosecute the pending applications related to the '866 patent. The record shows that, at that time, the USPTO once more raised the issue of inventorship with ImClone.

From a strategic viewpoint, one might argue ImClone was smart to hold on as long as it could to its position as licensee and co-inventor of the '866 patent. This enabled the firm to secure the billion dollar deal with Bristol Myers Squibb; and it may have enabled it to muddy the waters for the emergence of Amgen's rival human mAb, Vectibix. Because it also targets EGFR, Vectibix would almost certainly fall under the '866 patent when used in combination with chemotherapy. Amgen itself licensed the patent from Yeda virtually as soon as the New York decision was made.

ImClone is probably not yet in a terminal situation. Even though it will now have to pay Yeda royalties on Erbitux, this will probably amount to <2% of sales. There may, however, be market erosion of ImClone's position. Vectibix was approved shortly after the patent ruling and Amgen is planning to price the drug 20% cheaper than Erbitux. Without royalties to ImClone, Amgen will compete on price with its rival. Death by a thousand undercuts, perhaps? 

The next generation?

Second-generation biologics are now entering the marketplace.

For the best part of a decade, Amgen's Epogen has been the best-selling biotech drug. This situation has now changed with the appearance of two arthritis drugs—Centocor's Remicade and Immunex/Amgen's Enbrel at pole and second position. Although indicating that biologic products are making inroads in new markets, the change also reflects a more fundamental shift at the top biologic producers to phase in new 'second-generation' products that maintain market franchises.

Epogen was launched in 1989 with seven years' market exclusivity in the orphan indication of treating anemia in kidney dialysis patients. It has been the number one protein drug since 1996, but last year slipped off its pedestal to 7th place. Part of the explanation for this is that the anemia market is now divided among Epogen and two other erythropoietin (EPO) molecules: Johnson & Johnson's first-generation EPO, Procrit, and Amgen's second-generation EPO, Aranesp. The latter two products reached ~\$3.3 billion in sales last year compared with Epogen's puny \$2.5 billion!

Second-generation products, of course, make a great deal of strategic sense. Rather than pushing through a new treatment with a specialist sales force in a new indication, the goal is to consolidate a company's foothold in an existing market with an improved product that displaces both internal and external competition while maintaining the premium price structure justified by its original pioneering efforts. So, if you can pegylate, otherwise derivatize/formulate the original protein, claim a new composition of matter or demonstrate improved clinical

characteristics, then this R&D strategy is going to be more profitable than *ab initio* innovation in another indication or another mechanism of disease.

Humanized and human monoclonal antibodies (mAbs) are now also being touted as second-generation technologies. The theory is that the clinical performance of humanized/human mAbs will be superior to their chimeric antibody counterparts because of reduced immunogenicity and improved serum half-life.

Four of the ten best selling biologics in 2005 were mAbs. Two are chimeric: Remicade for rheumatoid arthritis and Rituxan for the treatment of B-cell leukemia both sold >\$3 billion worth in 2005. The other two are humanized: Avastin and Herceptin, with sales in the \$1–2 billion range.

With the September launch of Amgen's Vectibix, there is now a head-to-head contest between a chimeric and a human mAb directed against the same target. The chimeric incumbent under challenge from Vectibix is ImClone Systems' Erbitux. And yet Vectibix at launch will be priced ~20% lower than Erbitux.

Whatever the reasons for this price structure—and undercutting the competition could simply be a commercial move—this is not a pricing strategy that shouts "We have a better product than you." But the real proof of superiority of second-generation mAbs will only come from patient and clinician feedback. And of course the list of biotech's biggest sellers in years to come. 