Industry waits for fallout from Cabilly

Monoclonal antibody companies are eyeing their license agreements with Genentech after the US Patent and Trademark Office (USPTO) in February rejected a widely licensed patent, called Cabilly II, held by the S. San Francisco, California–based biotech. Genentech's appeal of the decision could drag on for up to a decade and many experts say the patent is likely to be invalidated in the end. The momentum against Cabilly II is encouraging licensees and potential licensees to consider ways to avoid royalty payments while the patent is in question.

Cabilly is one of the most ubiquitous patents in biotech. Nearly any company wishing to use host cell culture to make therapeutic recombinant antibodies has to obtain rights to the patent. There are 21 monoclonal antibody drugs on the market and nearly 40 in either phase 2 or 3 trials, many involving the Cabilly technology.

The original patent was issued in 1989 and was set to expire in 2006. But in 2001, the USPTO allowed Genentech to patent a continuation of Cabilly, dubbed Cabilly II, with an expiration date of 2018. The move angered many people in the industry who had endured the royalty burden for years. Pretax revenues from the Cabilly patents generated for Genentech more than $100 million in 2006 and $32 million in the first quarter of 2007, or $0.02 per share (**Table 1**).

In 2005, upon an anonymous request, the USPTO reexamined Cabilly II and rejected it on grounds of obvious-type double patenting—it was a blatant variant of what had been claimed in earlier patents, including Cabilly I (*Nat. Biotechnol.* **13**, 1329, 2005). Genentech appealed, leading to the second rejection in February 2007 of all 36 claims in the patent (*Nat. Biotechnol.* **25**, 272, 2007). Genentech can appeal one last time to a separate board in the USPTO, and if rejected again, the company will take its claims to the court system, according to a spokesperson. The process will take at least two years, but will likely drag on much longer, and in the meantime, Cabilly II remains valid. "Genentech has every incentive to delay this as long as possible," says Michael Siekman, a partner at Wolf Greenfield & Sacks in Boston, who estimates that the appeals process will probably last until 2013.

With two strikes against Cabilly II and many legal experts betting that in the end the patent will be struck down, antibody players are considering their options. "It's so obvious that it's a double patent," says Jennifer Seibert, director of intellectual property (IP) at YM Biosciences in Mississauga, Ontario. "I think it would make sense to stop paying royalties. But it's difficult for companies to make that call."

Halting royalty payments is tempting because it could save a bundle in fees. "It works just like insurance," says William Scofield, a partner at the law firm Lahive and Cockfield in Boston. "The question is, Do you pay the premium on the insurance policy and avoid the risk?"

The decision to take the risk or not partly depends on how confident licensees are that Cabilly II will be invalidated at the end of the appeals process. So far the odds seem stacked against the patent. Nearly all the supporting arguments for Cabilly II have been laid out already, and without new persuasive evidence, the board is unlikely to disagree with the USPTO's first two rulings, say legal experts. On top of that, a separate Supreme Court decision this year in the patent lawsuit *KSR v Teleflex,* which makes it easier to generally challenge patents based on obviousness, will likely make it easier to invalidate Cabilly II, as well (see p. 703).

But the fate of the patent is far from certain, experts caution. "You never know what the courts will say," says Alice Martin, a partner at the law firm Barnes & Thornburg in Chicago.

Adding to the uncertainty, Cabilly II is also embroiled in a lawsuit brought against it by MedImmune of Gaithersburg, Maryland, which has challenged the validity of the patent (*Nat. Biotechnol.* **25**, 264–265, 2007). The case is pending in a California district court and could be combined with Genentech's battle with the USPTO if that case is taken to the court system, say legal experts. (MedImmune has been acquired by the London-based pharmaceutical firm AstraZeneca.)

Plus, a licensee risks a lot if it gambles and loses. Anyone who stops paying Cabilly II royalties is at risk of being sued immediately by Genentech. If in the end the courts declare the patent valid, infringers could even be forced to stop making their products and pay triple damages for willingly disregarding their contracts. The risks are especially high for smaller biotechs who could be consumed by the distraction of a big lawsuit. "If Cabilly were upheld it could put you out of business," says John Morrow, president of Newport Biotech Consultants in Newport, Kentucky.

A less risky approach is trying to negotiate with Genentech or to work through legal avenues. Companies that have not yet licensed Cabilly II could try to include in new contracts a clause that says that if the patent is found unenforceable they get their

Genentech

Genentech (headquarters pictured here) received royalty payments based on the Cabilly patents of $105 million in 2006. Payments are estimated at up to $120 million for 2007.

Table 1 Major products for which Genentech receives Cabilly II patent royalties

Company	Drug	Type of monoclonal antibody; target	Indication first approved	FDA approval year
Hoffmann La-Roche (Basel, Switzerland)[a]	Rituxan (rituximab)	Chimeric; CD20	Non-Hodgkin's lymphoma	1997
	Herceptin (trastuzumab)	Humanized; HER2/ErbB2	Breast cancer	1998
	Avastin (bevacizumab)	Humanized; VEGF	Colorectal cancer	2004
MedImmune (now acquired by AstraZeneca, of London)	Synagis (palivizumab)	Humanized; F (fusion) protein on surface of respiratory syncytial virus	Prevention of RSV infection	1998
Centocor	Remicade (infliximab)	Chimeric; TNFα	Crohn's disease	1998
Abbott (Abbott Park, Illinois)	Humira (adalimumab)	Human; TNFα	Rheumatoid arthritis	2002
Wyeth (Madison, N.J.)/ Amgen (Thousand Oaks, CA)	Enbrel (etanercept)	Human; TNFα	Rheumatoid arthritis	1998
Imclone (New York)	Erbitux (cetuximab)	Chimeric; EGFR	Colorectal cancer	2004

[a]Hoffmann La-Roche has rights to these antibodies outside of the US.
CD, cluster of differentiation; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Source: Genentech SEC filings.

money back. Licensees could also try to set up an escrow account where their payments for Cabilly II would be directed until a final validity decision is made. Companies with IP may have some bargaining power if Genentech is interested in their technologies. Also, existing licensees should double-check the language of their contracts to see if there is any way their royalties are contingent upon the validity of the patent.

For companies that have licensed Cabilly II but have not yet brought a product to market, the best solution may be to do nothing, and hope the questions are resolved quickly. Inhibitex of Alpharetta, Georgia, for example, already shelled out $500,000 in an upfront fee to license Cabilly II for its phase 2 candidate, Aurexis. Inhibitex does not owe Genentech further payment until it receives FDA approval, and by then Cabilly II may be struck down. "That's the price you pay to be in the game," says Joe Patti, CSO of Inhibitex. "We could have waited [to take a license] until closer to market but the price is usually higher then, plus we wanted to have our licenses in place during our IPO [initial public offering]," he says.

Having licenses in place at the right time is crucial. Investors and potential acquirers want to know that a company has the proper IP and the freedom to operate, so for some, it may be best to pay the fees and move on. "It's always simpler if you can tell a pharma that you have the license," says Michael Braunagel, director of IP and licensing at Affitech in Oslo.

So far, at least, it is not apparent that anyone has made a move to halt royalty payments. The top Cabilly licensees have remained tight-lipped about their strategy going forward. "I think it comes down to people being risk averse," says Siekman. "There is a whole industry that hates this patent yet no one is willing to stick their neck out." There are disincentives for biotech executives to take such risks, adds Thomas Kowalski, a partner at the New York law firm Frommer, Lawrence and Haug. "Middle managers get dismissed if their decision results in being sued, and they do not necessarily get advanced or a raise if they save license and royalty fees."

Bringing down Cabilly II may mean more than just royalty fees to some. One worry is that Genentech might discriminate who can receive the Cabilly II license so that it may block out competitive products. Genentech has in the past been fairly consistent in handing out licenses, say experts, but there's nothing forcing the company to be evenhanded.

On the other hand, although most people in the field are rejoicing at the potential downfall of Cabilly II, the overthrow of a patent is a little disconcerting to biotechs with their own IP. Says Michael Zwick, vice president of business development at Neoclone in Madison, Wisconsin: "If you're a technology development company, you're looking at this and going, Why did this happen and could it happen to me?"

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