

Warning - Research Dollars at Risk!

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24 March 2003

[Legal Times](#)

IP law must support old patents and new research. Any imbalance threatens to shut down the new-drug pipeline.

Before the clinical trials are run, before the Food and Drug Administration approves, before hope is held out to millions of patients, new drugs start with scientists asking elemental questions about human life. Now the pipeline that leads from their laboratories through drug development to the FDA may be shut off at the source. Contrary to the interests of everyone, the moneys that fund small biotechnology companies and university labs could dry up.

The villain is a few seemingly unrelated judicial decisions and the increasing complexity of biotech research itself. Together they may serve to discourage the basic science on which medical advancement depends.

Biotech companies anchor one end of the pipeline that produces new drugs. Along with major universities, they perform the risky experiments that lead who knows where. They also develop the cutting-edge tools that permit this research - such as screening methods for new chemicals that might be transformed into medical cures and computer programs to better design those chemicals.

Then their patented ideas are licensed or sold to the large pharmaceutical companies. The strength of Big Pharma lies in refining those research results into the next generation of medical treatments and devices - and then selling them.

To keep the new drugs flowing, therefore, it is critical that patent law and practice support the ability of biotech companies and universities to stay in the lab. Unfortunately, the balance between the needs of patent holders and researchers may be upset.

DOING THE FDA'S WORK

Biotechnology is expensive to develop and depends on investments from venture capitalists and other angel investors. Those investments are made in large part because patent law ensures that the company doing the research will benefit monetarily from its results. Without patent protection, competitors could simply steal the fruit of millions of dollars of investment. Until recently, biotech companies and investors alike believed that patents would also shield the research tool technology around which these companies are often built.

In the last year and a half, however, the rug has been pulled out from under them. District courts have held that in certain circumstances, research on new drugs using U.S. patented tools does not infringe those patents under the "research exemption."

On Nov. 27, 2001, the U.S. District Court for the Southern District of New York applied the research exemption in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer Inc.*, 2001 WL 1512597. This statutory exemption (35 U.S.C. §271(e)(1)) states: "[I]t shall not be an act of infringement to ... use ... a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs." The court held that the use of four patented chemicals in developing a potential new drug was exempt from infringement. The court found that the relevant inquiry was whether it would "have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of [the] kinds of information that was [sic] likely to be relevant in the process by which the FDA would decide whether to approve the product."

Similarly, the U.S. District Court for Delaware stated on April 19, 2002, that "activities should only be found to exceed the scope of the §271(e)(1) exemption when they have no objectively reasonable application towards obtaining FDA approval." *Nexell Therapeutics Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197. Further, the court stated that "considerable leeway must be given to the defendant, because 'it will not always be clear to parties setting out to seek FDA approval for their new product exactly what kinds of information, and in what quantities, it will take to win that agency's approval.' "

Such language opens up the floodgate for free use of patented chemicals and methods by any company developing drugs for sale in the American market. If they can point, with "considerable leeway," to a "decent prospect" that the knowledge obtained will be necessary to win FDA approval down the line, then they need not worry about paying patent royalties.

Obviously, some drug companies may be helped in the short run. But a decrease in new drug candidates generated by biotech companies would eventually boomerang back on Big Pharma, causing their drug pipelines to shrink. Biotech companies will see the value of their patents - indeed, the value of their enterprises - questioned. Funding may dry up, and innovative ideas may be left by the wayside.

A case before the U.S. Court of Appeals for the Federal Circuit - *Integra LifeSciences Ltd. v. Merck*, Appeal No. 02-1052 - may provide some insight into whether that court will reverse such expansion of the research exemption or whether the Supreme Court or Congress will need to intervene. (The *Integra* case, which was argued in November 2002, had not been decided as of this writing.)

ON FOREIGN SHORES

In another blow to the owners of patents on research technology, the U.S. District Court for Delaware held on Oct. 17, 2001, that work performed outside the United States using U.S. patented technology does not infringe those patents if only the information resulting

from the work is imported into the United States. *Bayer v. Housey Pharmaceuticals*, 169 F. Supp. 2d 328. Yet the law (35 U.S.C. §271(g)) clearly states that "whoever without authority imports into the United States ... a product which is made by a process patented in the United States shall be liable as an infringer."

In *Bayer*, the use of a patented screening method to find a new chemical entity was held not to infringe the patent when only the description of the chemical was imported into the United States. Such information was held not to be a "product" under the statute. The fact that such information is precisely what the patented technology was designed to generate did not sway the court.

The *Bayer* decision means that basic research can be performed outside the United States essentially without concern for the rights of the U.S. patent holders. While American companies can obtain foreign patents, those won't help in countries without patent systems or with poorly enforced systems. In addition, the high cost of foreign patents means that companies are almost always forced to omit protection in some countries.

The end result is the same: The funding of U.S. entities developing basic biotechnology becomes more and more of a gamble.

'PHILOSOPHICAL CURIOSITY'

University laboratories, meanwhile, face an opposing crisis. Over the years, courts have developed an appropriate exemption to patent infringement for research pursued for "mere philosophical curiosity." In other words, when professors and students go into the lab to learn and discover for the sake of learning and discovery, their work is shielded from infringement claims. The benefits of encouraging academic research are thought to outweigh the patent holders' loss.

Now, an Oct. 3, 2002, decision from the Federal Circuit may chill the scientific work of universities. In *Madey v. Duke University*, 307 F.3d 1351, the court held that a university cannot just allege that it is performing research with no commercial end in mind. Given the modern coalition of academic and industrial interests, the Federal Circuit decided that the burden should be squarely placed on the university to prove that it has no commercial motive.

To be on the safe side, universities may have to assume that more projects do have a commercial motive. Then, just like industry, they will have to consider what patents might come into play. That's a huge undertaking. Every new experiment by a professor, or even a student, will call for a diligent analysis. A patent attorney should properly perform such analysis, but the expense could be tremendous. Yet if the university simply ignores patents, it could open itself up to lawsuits.

On the plus side, it is questionable what damages may be obtained for infringement occurring at universities, and the high costs of patent litigation may keep a lid on such suits. But the likely outcome is still that universities will be more cautious about what work is performed in their labs, perhaps chilling innovation and stemming new drug flow. And some patent owners may recognize this as an opportunity to shut down research long before any university spin-out company can be formed.

MORE OR LESS TELLING?

Taken together, these various court decisions have upset the balance as to when research should and should not be exempt from patent infringement claims. To ensure the continuing development of medical science, the biotech business may need to embrace new strategies.

One extreme solution is to protect new developments as trade secrets for a longer period of time until useful end products are actually identified and patented by the original researcher. That is, rather than develop a patent portfolio that can be licensed to others, the biotech company would become a full-service developer of new drugs, from basic research to marketable product. And all progress and methodology along the way would be kept secret from outsiders.

Of course, this is contrary to the whole concept of the patent system, which encourages scientists to disclose their innovations sooner rather than later. Moreover, such a strategy makes it difficult to persuade investors to provide support. It makes due diligence on the company more challenging and heightens the risk that just one ex-employee could open his mouth and undermine the company's entire business plan.

The success of this strategy depends on the ability of the company to fully develop and test the drugs on its own. That kind of work takes a huge amount of investment and requires biotech startups to establish strategic alliances with Big Pharma to survive. Will that paradigm be as potent for patients? No one knows.

Another less-than-attractive alternative is to patent everything in as many countries as possible. There are honorable competitors everywhere, and many within the United States will not risk infringement. The strategy requires significant funds to be set aside for development of the patent portfolio, but at least it makes clear what investors are buying into.

On the other hand, many countries have a much more expansive research exemption than the United States or a weaker system of patent enforcement (or both), so the value of obtaining such patents is questionable. Rivals may simply choose to do their research in countries with poor patent systems. Even now, more research laboratories are being built in Iceland.

A better compromise is a mixture of those two strategies. Biotech companies might want to set up a system of patent pools, which could license out the pure-research-type patents that are essential for development of new drugs in return for a royalty stream. A company could still keep to itself particular areas of research, but at the same time could better utilize the fruits of others' labor. This has worked well in the electronics field, and there is no reason it cannot work for drug development.

With regard to universities, infringement suits against academic targets are likely to seek injunctions rather than (difficult or impossible to prove) money damages. To shield their ongoing research, it is likely that universities will now demand indemnification against third-party infringement suits from any company having rights to develop and commercialize the university's research findings.

However, actual litigation against universities may not be very common. The current drop in biotech investment will discourage companies from spending too much on high-cost lawyering. And no company really wants the stigma of having sued professors. More likely, universities and biotech companies will find a different solution - licensing agreements that offer development rights to the professors' research results in exchange for royalties and the use of any patented research technology the professors need.

A STACKED SITUATION

Royalties themselves - and the related sublicensing fees - are becoming a real challenge in the biotech industry. Even as they perform their own original research, biotech companies are likely to be working with tools and products that others have patented. Big Pharma, in turn, works with the fruits of many smaller companies' research when it develops particular drugs. And each and every entity that contributed along the chain may have contracted to receive royalties off the (hopefully) wildly successful final product. This phenomenon is called "royalty stacking."

The danger is that biotech companies could get squeezed in the middle by excess royalty demands. From Big Pharma, biotech companies can expect a maximum royalty only in the neighborhood of 10 to 15 percent of net sales on a drug that is in a very early stage of development. That means there's a limit on the royalties and fees the biotech company can afford to pay other patent holders.

Consider this example: The biotech company receives a 12 percent royalty from Big Pharma on sales of a drug developed from the smaller company's earlier research. From that 12 percent, the biotech company must pay a 2 percent "reach-through" royalty to each of several research-tool patent holders; it must also fund its own work and turn a profit to reward its investors. Sometimes the numbers simply don't add up.

The same is true with regard to sublicensing fees. Such fees can run between 10 to 40 percent of what the biotech company would receive from Big Pharma. Thus, if the company owes more than three such fees on a particular line of research, it can't afford to pursue that research.

There is a maximum amount of royalties that can be paid for any one drug. Beyond that, no one will invest in its development. Greed by any one patent-owning entity can render groundbreaking research financially untenable.

Therefore, all patent holders have to recognize the need to reduce royalties to protect everyone's ability to create new drugs. Sometimes patent pooling will help to reduce royalty costs. At other times, patent holders may need to ask an independent arbitrator to split the total royalty on a particular drug.

FOCUS ON THE LAB

There is a disaster waiting to happen in the therapeutic industry. Investment dollars are not flowing, the drug pipeline is shrinking, and recent court decisions are not going to help. A new paradigm is required where innovative companies compete and cooperate.

Gone are the days when broad exclusivity was necessary. Patents expire after 20 years, and that is too short a time for a single biotech company to exploit a whole field. The law (and the future) may be too uncertain to properly calculate damages when research patents are infringed. And too many investment dollars have already been diverted into the coffers of lawyers to bring and defend ultimately destructive litigation.

One need not look far to see the consequences of a wasteful fight. In the battle between Sibia Neurosciences Inc. and Cadus Pharmaceutical Corp. over a research tool patent, only the attorneys won. The lawsuit began in 1996. So much money was spent that both companies were severely weakened. Although Cadus eventually won before the Federal Circuit in September 2000, it had already sold off most of its drug discovery assets the previous year. Also in 1999, Sibia chose to merge into industry giant Merck & Co.

There is a big philosophical issue here: Are patents on basic research tools a good thing? Would that kind of research continue without the full protections of the patent system? Our forebears did not distinguish among types of innovation; should we? How do we best encourage scientific discovery, given the needs of those who labor to develop new research tools and those who labor to research new drugs? If the Federal Circuit can't find the right balance, Congress will have to step in.

But the bottom line is that the biotech industry must change - to adapt to the new court decisions, to strengthen the drug pipeline, to focus efforts on innovation and not litigation. A new breed of executives must pursue more cooperation to keep the medicine coming.

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