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When Patents Became Interesting in Clinical Research

By Norman M. Goldfarb

Few experienced clinical trial agreement lawyers and negotiators have ever seen the intellectual property section invoked by an investigator's discovery or invention. Nevertheless, it has evolved into perhaps the most complex and contentious section of the agreement. As a result, many thousands of hours are consumed every year negotiating it.

When asked why the section is so important, people in the industry most commonly cite three examples where the intellectual property language was very important: Rogaine, Propecia and Viagra. Given these examples, pharmaceutical companies and research institutions insist on protecting their rights to the next bonanza. However, as it turns out, the examples tell a different story.

Rogaine

In 1965, Upjohn (now part of Pfizer) discovered that a piperidino-pyrimidine derivative, later named minoxidil, was a powerful vasodilator in dogs. It hypothesized that it might prove to be a valuable treatment for hypertension in humans. It obtained a patent on the drug two years later. After FDA approval 14 years later, in 1979, Upjohn marketed it under the trade name Loniten. In the meantime, however, minoxidil found another use.

Back in 1967 or 1968, Charles A. Chidsey, MD, Associate Professor of Medicine at the University of Colorado School of Medicine, starting conducting the first of two studies on minoxidil in hypertensive patients, as the sole investigator. (Gilmore, E, Weil, J, and Chidsey CA. Treatment of Essential Hypertension with a New Vasodilator in Combination with Beta Adrenergic Blockade, NEJM 282: 521-527, 1970) During the second study, in 1970-71, he noticed unexpected hair growth on the faces and shoulders of some of his women subjects. A male subject experienced hair growth on the bald part of his head. The growth was so noticeable that his barber said "Boy, you better find out what you're taking for your high blood pressure!" (Gottlieb, TB, Katz, FH, Chidsey, CA Combined Therapy with Vasodilator Drugs and Beta Adrenergic Blockade, Circulation XLV, 571, 1972)

Puzzled, Dr. Chidsey asked some endocrinology and dermatology colleagues if they could help him determine the mechanism of the phenomenon. Dr. Chidsey met with Guinter Kahn, MD from the Division of Dermatology. One of them raised the idea that a topical application may be useful in treating baldness. Dr. Kahn offered to experiment with hairless mice to elucidate the mechanism. Dr. Chidsey contacted Upjohn and obtained permission to give Dr. Kahn minoxidil for this use. Unbeknownst to either Dr. Chidsey or Upjohn, Dr. Kahn and his resident, Paul J. Grant, MD, instead applied the minoxidil to the skin of various staff members in an emulsion covered by a bandage. The results were positive.

Drs. Kahn and Grant conducted this experiment without an IND, approval (or even knowledge) by the University's Clinical Research Committee (chaired by Dr. Chidsey), or informed consent. (The National Research Act did not create Institutional Review Boards until 1974.) There almost certainly was no contract between Upjohn and Drs. Kahn and Grant.

Drs. Kahn and Grant did not inform Upjohn of the positive results, preferring instead to file a patent application. When Dr. Chidsey became aware that Drs. Kahn and Grant intended to

file the application in the summer of 1971, he contacted Upjohn. He had to work his way up to David Weissblatt, President of the company, before Upjohn agreed to proceed with its own patent application in the fall of 1971 as a precautionary measure, with Dr. Chidsey as inventor.

The patent applications languished until the 1980s. Upjohn finally became interested in the commercial opportunity, and a patent interference action ensued in the mid-1980's. A consolidated patent (U.S. #4,596,812 Charles A Chidsey, III and Guinter Kahn) issued in 1986, with Upjohn as the owner. Between the date the FDA approved this use of the drug in 1988 and the date the patents expired in 1996, royalties totaled over $33 million on $700 million or more in sales of…Rogaine.

$33 million is a big number, although not compared to $700+ million. The Rogaine story is unique in many respects, and therefore not a precedent for much of anything except drug accountability. For example, Drs. Kahn and Grant proved efficacy of the topical application in a renegade experiment that Upjohn and the University did not even know about. It was only with the cooperation of Dr. Chidsey, who conducted his studies with no intellectual property agreement with Upjohn, that the company had any leverage in the negotiation with Drs. Kahn and Grant. It is hard to imagine a similar scenario playing out today.

Propecia

In 1992, the FDA approved Merck's Proscar (finesteride) to treat prostate enlargement. Some patients observed a side effect – stabilization or even reversal of male pattern baldness. Clinical trials determined that finesteride was effective for treating baldness at a much lower dose than in Proscar. In 1998, the FDA approved finasteride as a hair-loss treatment. Merck now markets it under the brand name Propecia.

Not knowing the pharmacodynamics, it is surprising that no-one noticed Propecia's affect on hair growth until after the product was marketed. Thus in this case, the language in the clinical trial agreement was irrelevant because the key discovery was made with the marketed drug, and the use patent could have issued to any alert member of the public.

Viagra

In 1989, Pfizer chemists in Sandwich, England synthesized sildenafil citrate and named it UK-92,480. Originally intended for the treatment of hypertension, preclinical testing indicated that it had more potential as a treatment for angina pectoris. Clinical trials started in 1992, with negative results for that indication. A ten-day dose-tolerance study in Merthyr Tydfil, Wales with healthy volunteers showed negative results at the expected therapeutic dose of 25 mg. In a conference call, one of the investigators mentioned that, at a dose of 50 mg, side effects appeared, including indigestion, backache and penile erection. The observations were routinely recorded and discussed. After two years of unenthusiastic laboratory experiments and market research, Pfizer began clinical trials for erectile dysfunction at the 50mg dose in 1994. Surprisingly positive results were observed. The FDA approved UK-92,480, now known as Viagra, in 1998. Pharmacists filled 2.9 million prescriptions in the first quarter after approval.

This discovery occurred during a Phase I study, so it is a precedent for intellectual property language in Phase I clinical trial agreements. However, it is even more of a precedent for paying attention to adverse events; it apparently did not occur to anyone for some time that a blockbuster drug had been discovered.

Conclusion

Commercially valuable inventions and discoveries by investigators during clinical trials, especially in later-stage studies, are very infrequent. In fact, the aggregate value of the labor spent negotiating intellectual property language may exceed the value of the inventions and discoveries. With roughly 40,000 multicenter studies per year, the labor cost of negotiating the intellectual property language probably runs into the tens of millions of dollars. The opportunity cost in study delays is probably even larger. A more accommodating attitude by both sponsors and sites may be appropriate. In fact, an insurance company may be willing to sell policies to cover the potential royalties, at a cost far less than the time spent negotiating the clinical trial agreements.

Note

The above accounts rely on incomplete documentation and personal interviews that may not be accurate. Drs. Kahn and Grant declined to comment for the article.

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