BUSINESS AND REGULATORY NEWS

Company, academics argue over data

Immune Response (Carlsbad, CA) has started arbitration proceedings against medical researchers at the University of California (San Francisco) and Harvard University (Cambridge, MA) over publication of negative data from a phase III trial of the firm's anti-HIV drug Remune. Opinion is mixed as to whether or not the company has tried to manipulate unfavorable clinical trial data about a potential blockbuster drug, or whether the university researchers have violated a research agreement. The dispute raises questions about inherent conflicts of industry-supported medical research, and highlights the lack of regulatory oversight of research contracts between academia and industry.

Remune, a disabled form of HIV (HIV-1 immunogen), was supposed to stimulate the body to produce more antibodies to fight the active virus. But analysis of a three-year study of 2,527 patients has found that Remune is no more effective than placebo at reducing disease progression. Designed as a "real-world" test, the study looked at patients who may have been switching to, or already taking, other drugs with a different mechanism of action, such as protease inhibitors, according to the study's lead researcher, Joseph Kahn, associate professor of medicine at UCSF. Patients receiving Remune showed no difference in viral load and a clinically insignificant change in CD4 cell counts compared with the control group. Consequently, an independent review board halted the study in May 1999 before it was completed, and Kahn and Stephen Lagakos, professor of biostatistics at the Harvard School of Public Health, began preparing to submit the results to the *Journal of the American Medical Association*.

However, Immune Response, which has spent $191 million since 1986 on developing and testing Remune (its only drug in phase III trials), claims its own statistical analysis of a random subset of 252 patients who had blood samples taken more often (3 months) than in the main study (6 months) show some benefit from taking Remune. The company says viral load was "significantly" lower in Remune patients compared with the control group.

Kahn says he included these data in his manuscript, but refused to include Immune Response's analysis of the data because it was not part of the original protocol. Kahn also says that the researchers own analysis of that data did not show a benefit of Remune in this subset. "This is not data that can be reanalyzed," says Kahn. "Their analysis was post-hoc and unspecified. We felt we had to stay firm about using the statistical methodology that we specified up front."

Immune Response tried to assert right of ownership over the entire dataset, and informed Kahn and Lagakos in January 2000 that it would not provide them with the final dataset for the study. Kahn and Lagakos, however, used interim data from the independent Data Safety Monitoring Board (accounting for 95% of the results) and submitted the paper. Immune Response began legal proceedings against the pair on September 1, but the paper was published in *JAMA* on November 1, prompting a 25% fall in Immune Response share price to $4.63. A week later, shares were still trading at $4.78, down 73% from the 52-week high of $18.31 in March and knocking $39 million off the firm's market capitalization.

Immune Response is claiming damages of $7 to 10 million as a result of the *JAMA* publication. "We felt that involvement of a third party through arbitration was the only way to ensure that all parties, including the clinical trial investigators, would have input on what would be published," vice president Ronald Moss said in a statement. The company's claim will be heard by the American Arbitration Association, a third-party alternative to civil court in California.

While officials at Immune Response would not speak to *Nature Biotechnology*, Agouron Pharmaceuticals (La Jolla, CA), co-developer of Remune and subsidiary of drug giant Pfizer, stands by Immune Response, and analysts Alan Auerbach of First Security Van Kasper (Los Angeles, CA) trusts their judgement. "If there isn't [any effect on patients], why is Pfizer putting so much money into this?" asks Auerbach. "Are you telling me that Jim Kahn is smarter than Pfizer? I have a problem believing that."

But Charles Engleberg, a biotech analyst at Americal Securities (San Francisco, CA), says he's had a sell recommendation on Immune Response for three years because of his underlying skepticism about how Remune is supposed to work. "The patients have huge viral loads and giving antibodies isn't going to make a difference," says Engleberg. "I've been following this since 1993 and the company has been guilty of massaging data all along and all our clients know it."

A similar incident occurred in August 1997, when Knoll Pharmaceuticals (Mt. Olive, NJ), a subsidiary of BASF, agreed to pay up to $135 million to settle allegations that it tried to suppress research showing its prescription thyroid drug Synthroid is no better than cheaper alternatives—a study that was published in *JAMA* in April 1997. Knoll had threatened a lawsuit to stop its publication, and Betty Dong, a UCSF researcher who conducted the study, told the journal that Knoll had suppressed her findings for more than six years. Biomedical firms cover up unfavorable clinical data "more often than not," claims Kahn, "We just don't hear about it."

Richard Jennings, director of the Wolfson Industrial Liaison office at Cambridge University, points out the inherent conflict between profit-seeking companies and truth-seeking researchers who rely on them for funding. "It's a difficult ethical issue," says Jennings. "The company is trying to make the best of results with analysts breathing down their necks, while scientific researchers also feel the heat. There is major pressure for things to get perverted."

Nevertheless, there is currently no governmental oversight of research agreements between companies and universities. It is generally understood that if a company has paid for the research, it owns the data, but it can't restrict researchers from publishing. For instance, Cambridge University (Cambridge, UK), which receives about £18 million ($27 million) research funding yearly from private industry, has its own guidelines that allow publication of all data as long as sponsors have advance notice of the findings. So far, Cambridge has avoided the kind of conflict that has occurred at UCSF but, says Jennings, "No system is perfect."

Moreover, a Stanford University study, published in the same issue of *JAMA*, has found that 60% of the US's top research universities lack specific guidelines governing relationships between private companies that pay for research conducted on campus (**284**, 17, 2000). This lack of clear guidance can cause confusion among industrial partners, competition among universities for corporate money, or erode academic standards, according to study author Mildred Cho, a research fellow at Stanford's Center for Biomedical Ethics. Cho recommends extending some kind of federal oversight to industry-academic research agreements, similar to the kind given to patient consent for human experimentation. She says the disputes involving Dong, and now Kahn, have come out into the open "only because these researchers and institutions were willing to risk multimillion settlement to get information out there—most people are not willing to do that."

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