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Technology Transfer:

Will Exercising Bayh-Dole's 'March-In' Provision Open Pandora's Box?

By Jennifer Van Brunt
Editor

By petitioning the U.S. Department of Health and Human Services (HHS) to invoke the "march-in" provision of the Bayh-Dole Act, **CellPro Inc.** may have opened the lid on Pandora's box. Far from being an isolated case of a small company seeking its own brand of justice against the might of a large pharmaceutical company, the case has far-reaching implications for technology transfer and the perceived value of collaborations between industry and universities.

It means the federal government can take control of any license granted on federally funded research if it deems the situation warrants it — and, therefore, that no license is sacrosanct.

The specter of the "march-in" provision — which authorizes the HHS secretary to issue licenses to technology developed with federal funds, even if a company already holds patent rights to the technology — has sent massive shudders throughout the American university technology transfer community. This collective apprehension also is felt by the biotechnology companies and large pharmaceutical houses that depend on basic inventions from university labs to fuel their own drug discovery efforts. On top of that, many biotechnology companies rely on the exclusivity of the licenses they hold to attract pharmaceutical partners. These licenses can in fact be the key to a collaboration, and financial support from a big pharmaceutical partner can often be the key to survival for a small biotech firm. Without some guarantee of exclusivity, the reasons for partnering in the first place come under question.

At the heart of the matter is a cell-separation device — or, rather, two such devices — used to purify stem cells by processing a patient's peripheral blood or bone marrow cells *ex vivo*. But it's the particular monoclonal antibodies (anti-CD34 antibodies) used in these devices to separate the stem cells that are the source of contention. The parties — CellPro on the one hand and **Baxter Healthcare Corp.** (NYSE:BAX), **Becton Dickinson & Co.**, of Franklin Lakes, N.J., and **The Johns Hopkins University School of Medicine**, of Baltimore, on the other — have been in patent infringement proceedings for about five years.

One device, the Ceprate SC Stem Cell Concentration System, is manufactured and sold by CellPro (NASDAQ:CPRO). The FDA approved the Bothell, Wash., company's device in December 1996 for purifying stem cells from cancer patients prior to chemotherapy, radiation or bone marrow transplantation. The separated cells are returned to the patient after

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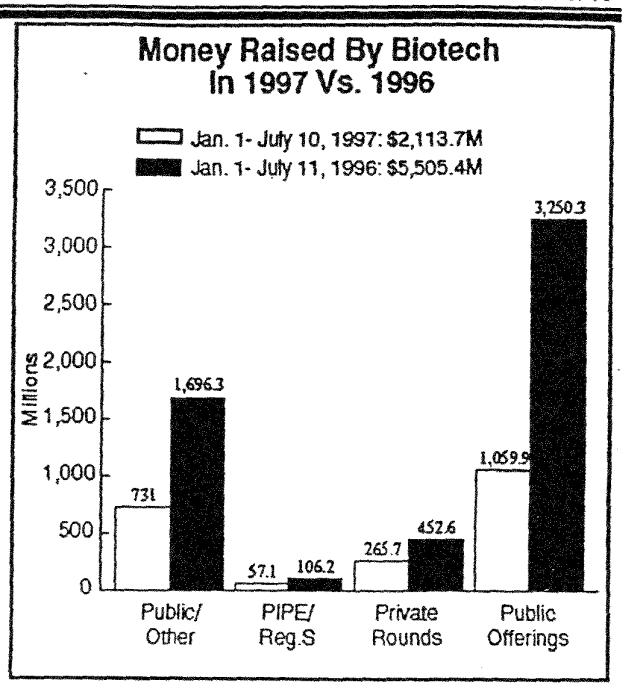

10 BIGGEST GAINERS FOR THE WEEK

(By Percent)		(By Dollars)	
Titan Pharma	+37	Qiagen	+9.000
Cortech	+37	Parexel Intl	+5.625
Novavax	+32	Incyte Pharm	+5.000
Targeted Genet	+31	Centocor	+3.938
Gliatech	+22	Sonus Pharma	+3.875
Genelabs	+20	Zonagen	+3.750
Qiagen	+18	SangStat Med	+3.500
Parexel Intl	+18	Agouron	+2.875
Noven	+17	Affymetrix	+2.563
Biocircuits	+17	Emisphere	+2.500

10 BIGGEST LOSERS FOR THE WEEK

(By Percent)		(By Dollars)	
British Biotech	-27	British Biotech	-10.125
GeneMedicine	-26	Triangle Pharma	-3.750
UroCor	-19	Teva Pharm	-3.125
Triangle Pharma	-16	Amgen	-2.766
Collab. Clin. Res	-16	Dura Pharm	-2.688
Creative Bio	-14	Genzyme	-2.563
Alteon	-14	Gilead Sciences	-2.500
DepoTech	-13	Vertex Pharm	-2.437
Immucor	-13	Pharma Prod Devlp	-2.188
Xenova Group	-13	Interneuron	-2.000

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one of these procedures to help restore the patient's blood and immune systems, which are impaired or destroyed by aggressive therapy or disease. CellPro's device, which uses an avidin-biotin immunoaffinity cell-selection system, takes advantage of monoclonal antibodies to positively select the cells of interest or negatively deplete unwanted cells.

The second stem-cell selection device is manufactured by Baxter; Baxter's Isolex 300 magnetic cell-selection system also relies on monoclonal antibodies to pluck out the cells of interest from peripheral blood. Johns Hopkins holds patents on the CD34 monoclonal antibodies used in the device; the university licensed the patents to Becton Dickinson which in turn licensed therapeutic applications to Baxter. The FDA's Biological Response Modifiers Committee is scheduled to review the Isolex device on July 24, but Baxter, headquartered in Deerfield, Ill., already has been selling the device abroad for a number of years.

As well, Baxter recently signed a major agreement with **VIMRX Pharmaceuticals Inc.**, of Wilmington, Del., to form a new business using the same Isolex device in *ex vivo* cell and gene therapy — areas outside the main focus of Baxter's business.

"Baxter saw a large number of potential applications to take the technology to the next level," explained Deborah Spak, Baxter spokeswoman. The Baxter-VIMRX cell therapy venture, valued at about $120 million, is not only the richest of all of VIMRX's recent partnerships, but also the most prominent. With the ongoing patent litigation over the monoclonal antibodies used in the device, it may also become the most controversial.

Baxter and its co-plaintiffs have argued that CellPro's product infringes their patents. To make a long story short, although a federal jury originally ruled in CellPro's favor in August 1995, a U.S. district judge overturned that verdict in March 1997 and agreed with Baxter, awarding it $2.3 million in damages. Moreover, because the jury concluded that CellPro's infringement was willful, the judge could award treble damages to Baxter and the co-plaintiffs.

Baxter and its co-plaintiffs have sought an injunction to bar CellPro from selling its product; in retaliation, CellPro has petitioned HHS to invoke its privileges under the Bayh-Dole Act. According to Baxter's Spak, the federal judge may reach a decision regarding the injunction (as well as the question of enhanced damages and $7 million in attorneys' fees) in the next month or so. Until that time, CellPro can't appeal the decision, explained company spokeswoman Joann Reiter.

Meanwhile, HHS Secretary Donna Shalala has turned the matter over to the National Institutes of Health (NIH), which has accepted documents from each party in the dispute so that it can conduct an informal fact-finding investigation before it reaches a decision — for which there is no built-in time frame. But NIH will decide whether to proceed to the next stage in the process by early next month, according to Reiter.

There is no historical precedent for this; in fact, although in the past there have been instances of companies petitioning HHS to intervene in licensing negotiations, most have been frivolous; there has never been a case where the HHS has directly ordered a license to federally funded technology.

The Bayh-Dole Act of 1980, named after former U.S. Senators Birch Bayh (D-Ind.) and Robert Dole (R-Kan.), granted universities the right to patent discoveries from federally funded research and to license those inventions to private companies for commercial development. In fact, the act not only required that universities file patents on the inventions they elect to own, but it actually encouraged them to participate in technology transfer activities.

Since its inception, the Bayh-Dole Act has indeed made a dramatic impact on university research and on the economy in general. According to a five-year survey conducted by the Association of University Technology Managers (released in February 1997), prior to 1980, fewer than 250 patents were issued to U.S. universities every year; by 1995, that number was up to about 1,500 issued patents annually. As well, universities have begun to leverage their partnerships with industry; according to the survey, 76 U.S. universities attracted nearly $113 million in new industry-based research support in 1995. In that same year, academic institutions earned close to $424 million in royalties. On a broader scale, the survey found that licensing of university inventions adds more than $21 billion to the economy and supports 180,000 jobs each year. Moreover, in 1994 and 1995, a total of 464 companies were started as a result of academic licensing.

Thus, the Bayh-Dole Act provides incentives for both universities — to market their inventions — and industry — to make high-risk investments. A company that licenses a tech-

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Biotech Company** (Country)	Pharma Company (Symbol/Country)	Type/Product Area	Amount	Terms/Details (Month)
Cytel Corp.	Schwarz Pharma AG (Germany)	Termination of 12/95 collaboration to develop carbohydrate selectin blockers, including Cylexin (currently in Phase II trial for preventing reperfusion injury in infants undergoing heart bypass surgery for congenital defects)	ND	Both companies agreed that the market for the product in its current indication is not large enough to share (in 6/96, Cylexin failed in Phase II trials for reducing reperfusion injury in heart attack patients receiving angioplasty); Cytel retained rights to Cylexin (5/97)
Xoma Corp.	Pfizer Inc. (NYSE:PFE)	Termination of 6/87 development and marketing agreement on monoclonal antibody E5 for treating Gram-negative sepsis	ND	The termination follows Pfizer's decision in 4/97 to discontinue U.S. Phase III clinical trials due to lack of clear efficacy; all product rights revert to Xoma (6/97)

NOTES:

This chart contains information on modified and terminated agreements only, covering the time period between 3/22/97 and 6/24/97. It does not include arrangements that are classed strictly as production, marketing and/or distribution agreements, nor does it include any collaborations that involve agricultural product development.

For a chart listing new collaborations between big pharma and biotech companies for the same time period (4/97 - 6/97), see the 6/30/97 issue of *BioWorld Financial Watch.*

ND = Not disclosed, reported and/or available

* Private companies are indicated with an asterisk.

** Unless otherwise noted, the trading symbols for public biotechnology companies can be found by referring to the BioWorld Stock Report For Public Biotechnology Companies on pp. 9-10.

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nology from a university makes a considerable investment to turn that into a marketable product, but it makes that investment with the assumption that it has an exclusive license. If the federal government can preempt that license, there is likely to be a chilling effect on university transfer activities.

"There's a general sense in the technology transfer community that this is not an appropriate circumstance [in which to invoke Bayh-Dole's 'march-in' provision]," explained **David Aston**, the associate director of the University of California Office of Technology Transfer. The CellPro petition is "a litigation tactic," whereas the intent of the "march-in" provision is to cover situations in which there is a question of public safety or health involved, he continued.

For instance, if for some reason a company takes an exclusive license on a university patent and then fails either deliberately or through gross neglect to make a product using that technology — and there is some public interest issue involved — that would be the appropriate situation under which to invoke the "march-in" provision. As well, "under patent law, the government has the option to infringe any patent it wants to (although it may be required to pay a royalty) for reasons of national security, or in a time of war or natural disaster, for instance. The national interest overrides the patent system." But this is not one of those situations.

CellPro argues that since its device is the only FDA-approved product on the market, removing it would indeed raise issues of public health for cancer patients awaiting bone marrow transplants. Johns Hopkins, however, has since assured HHS that patient access to stem cell selection technology is not at risk. Hopkins, Baxter and Becton Dickinson have asked the federal court to delay any injunction to remove CellPro's device from the market until Baxter's Isolex 300 system is approved by the FDA.

"Companies have always been a little skittish about the government's rights [to technology developed with government funds] when they take an exclusive license," explained **Nina Ossanna**, the associate director of the Office of Technology Licensing for Johns Hopkins' School of Medicine. But until now, she continued, the tech transfer office has always been able to assure company officials that there has never been an instance when the government has exercised its march-in rights.

The CellPro petition is the "first serious challenge to Bayh-Dole, and companies are concerned," Ossanna continued. If CellPro is successful in its challenge, "it will put a lot of fear into companies considering licenses," explained Ossanna. There may be a Bayh-Dole challenge lurking in the future that will have to be overcome.

"If the government does exercise the 'march-in' provision, it will seriously undermine the licensing efforts of universities," Aston added. ■