NATIONAL INSTITUTES OF HEALTH
OFFICE OF THE DIRECTOR

DETERMINATION
In the Case of
PETITION OF CELLPRO, INC.

The National Institutes of Health (NIH) has determined that the initiation of march-in procedures, as requested under the petition outlined below, is not warranted at this time. NIH retains jurisdiction over the instant proceedings until such time as a comparable alternative product becomes available for sale in the United States.

The CellPro Petition

On March 3, 1997, CellPro, Incorporated (CellPro) filed a petition with the Secretary of Health and Human Services (Secretary) requesting that the Government exercise march-in rights under the Bayh Dole Act (Act), 35 U.S.C. §§ 202-212, in connection with certain patents owned by The Johns Hopkins University (Hopkins) and licensed first to Becton-Dickinson and then to Baxter Healthcare Corporation (Baxter).[1] As discussed in greater detail below, the march-in provision of the Act authorizes the Government, in certain circumstances, to require the contractor (or grantee) or its exclusive licensee to license a Federally-funded invention to a responsible applicant on reasonable terms, or to grant such a license itself. CellPro asserts that such action is necessary to alleviate health or safety needs that have arisen because the United States District Court for the District of Delaware (Court) has found the stem cell separation device developed by CellPro, the Ceprate SC, to infringe two of the patents in question and has enjoined its sale.[2] Alternatively, CellPro asserts that march-in is warranted because Hopkins and Baxter have failed to take reasonable steps to commercialize the technology. At the present time, CellPro is the only company that has an FDA-approved device commercially available.

The Department of Commerce regulations implementing the Act are set forth at 37 CFR § 401.6. According to § 401.6(b):

> [w]henever an agency receives information that it believes might warrant the exercise of march-in rights, before initiating any march-in proceedings, it shall notify the contractor in writing of the information and request informal written or oral comments from the contractor, as well as information relevant to the matter.

The regulations provide that "the agency shall, within 60 days after it receives the comment, either

---

[1] These patents are: U.S. Patent No. 4,965,680; U.S. Patent No. 5,130,144; U.S. Patent No. 5,035,994 and U.S. Patent No. 4,965,204.

[2] The Order for Permanent Injunction and Partial Stay of Injunction (Order), entered July 24, 1997, includes a partial stay allowing CellPro to continue selling its device under certain restrictions. CellPro has indicated that it intends to appeal the Court's ruling.

initiate the procedures below or notify the contractor, in writing, that it will not pursue march-in rights on the basis of the available information." Id. Pursuant to § 401.6, the NIH, which has the delegated authority to make the march-in determination in this case, notified Hopkins of the petition and requested comment. Hopkins made its initial response on May 7, but in the interim, CellPro had made an additional submission to which Hopkins sought to respond. In sum, CellPro made supplemental filings on April 24, May 8, May 28 and July 2. After its initial response on May 7, Hopkins made supplemental filings on May 19, June 2 and July 2. Because the parties continued to make submissions and insist on the right to comment on the submissions of the other party, the NIH informed the parties that the 60 days set forth in the regulations for a determination by the agency would be calculated from June 2nd, but agreed to review and consider any submissions made by the parties through July 2.[3]

The administrative record in this matter consists of the submissions of the parties, letters from universities, corporations, members of Congress, and other members of the public on this issue, as well as other pertinent materials obtained by the NIH.

Statutory Background and Criteria

The stated policy and objective of the Bayh-Dole Act is:

> to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

Act at § 200. Toward this goal, the Act addresses not only rules governing the licensing of Government-owned inventions, but also addresses Federal contractors'[4] rights to elect title to inventions made with Federal funding. In giving Federal contractors the right to elect title to inventions, Congress altered the preexisting scheme under which the funding agency generally owned patentable inventions made with Federal support unless the contractor obtained a waiver. Congress believed that this change would promote the utilization and commercialization of

---

[3] Hopkins made an additional submission July 29, which was not considered by NIH.

[4] Defined in the Act as "any person, small business firm or nonprofit organization that is a party to a funding agreement," Act at § 201(c). In 1983, President Reagan issued a memorandum instructing all Federal agencies, to the extent not prohibited by law, to grant all recipients the same right to their inventions as the Bayh-Dole Act provided small businesses and nonprofit institutions.

inventions and would harmonize Federal patent policies. See Senate Rep. No. 96-480 at p.3.

In giving contractors the right to elect title to inventions made with Federal funding, the Act also includes various safeguards on the public investment in the research. For example, the Federal agency retains a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world. See 35 U.S.C. § 202(c)(4). In addition, the Act includes march-in rights, which provide a Federal agency with the authority in certain, very limited circumstances, to make sure that a federally funded invention is available to the public. Section 203(1) states:

> With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such--
>
> > (a) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;
> > (b) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;
> > (c) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or
> > (d) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204.[5]

Jurisdiction

In its submissions, Hopkins suggested that NIH did not have jurisdiction in this matter. CellPro

---

[5] The legislative history to the Act indicates that Congress anticipated that third parties, such as CellPro in this case, would be likely to inform the Government of the possible need for march-in. However, it is clear that march-in remains a purely government authority. Senate Report No. 96-480 states that:

> "[m]arch-in" is intended as a remedy to be invoked by the Government and a private cause of action is not created in competitors or other outside parties, although it is expected that in most cases complaints from third-parties will be the basis for the initiation of agency action.

disagreed. It is our conclusion that NIH has jurisdiction to determine whether to exercise march-in with respect to the patents in question. The patents which were found by the Court to be valid and infringed are U.S. Patent Nos. 4,714,680 ('680 patent) and 4,965,204 ('204 patent). Documentation submitted by Hopkins clearly establishes that the inventions claimed in these patents were funded by the NIH. For instance, with regard to the '680 patent, Hopkins submitted to the NIH a letter dated October 4, 1984, notifying the NIH that Hopkins had elected title to the invention. In addition, Hopkins provided annual utilization reports filed during the 1980's and early 1990's, and a license from Hopkins to the U.S. Government, which expressly acknowledges that "the invention was made in the course of research supported by the DHHS."[6] Since the inventions were funded by the NIH, as acknowledged by Hopkins well before the patent dispute with CellPro arose, there is a clear presumption of jurisdiction by the NIH, and Hopkins has not submitted sufficient evidence to rebut that presumption.

Decision

The NIH has evaluated the administrative record with regard to two prongs of the statutory criteria, 35 U.S.C. § 203(1)(a) and (b). The NIH has examined whether, (1) Baxter has failed to take, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject inventions; and, (2) there exists a health or safety need which is not reasonably satisfied by Hopkins or Baxter.[7] Based on these criteria and the available information, march-in is not warranted at this time.

Practical Application of the Subject Inventions

Practical application is defined under 37 C.F.R. § 404.3(d) as "to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms." The administrative record demonstrates that Hopkins and Baxter have clearly met this standard.

---

[6] Although these documents relate specifically to the '680 patent, the '204 patent states that it is a divisional application of the application, serial number 670,740 (the '740 application), from which the '680 patent issued. The claims in the '204 patent are, therefore, based on the original disclosure that was contained in the '740 application, as to which Hopkins had elected title. The other two patents also involved in the patent litigation, U.S. Patent Nos. 5,035,994, and 5,130,144, also issued from divisional applications of the '740 application.

[7] The two other prongs are clearly not relevant. Subparagraph (c) narrowly applies to "public use" required by particular laws. CellPro has not claimed any such law to be applicable in the present case, nor does NIH believe any to be applicable. Subparagraph (d) authorizes march-in when an exclusive licensee of a subject invention has failed to agree (or obtain a waiver of such requirement) that any products embodying the invention or produced through the use of the invention will be manufactured substantially in the United States. Baxter has agreed to manufacture substantially in the United States.

This technology was originally developed in the laboratory of Dr. Curt Civin at Hopkins and first published in 1984. Hopkins filed for patent protection and was awarded four patents, the first of which issued in 1987. The technology was first exclusively licensed to Becton-Dickinson & Co. (BD). BD began marketing the first anti-CD34 antibody in 1985 and has sold anti-CD34 antibodies worldwide ever since. Since BD was only interested in the diagnostic applications, the company exclusively sublicensed therapeutic rights to Baxter. Baxter began development of a therapeutic system and sublicensed rights to Applied Immune Sciences (now part of RPR Gencell) and Systemix (now part of Novartis). Baxter also held licensing discussions with CellPro, but no license agreement was signed.

By late 1991, Baxter had developed a prototype stem cell selection device. In 1992, Dr. Civin began clinical trials with the device, and Baxter started its own clinical trials in 1993. In January 1995, Baxter's Isolex 300 System received regulatory approval in Europe (CE Mark of Conformity for Medical Devices). In the United States, Baxter's systems have been installed in numerous transplant centers over the past three years; the Baxter device has been used in clinical trials to process peripheral blood and bone marrow for hematopoietic reconstitution in patients. On February 24, 1997, Baxter filed for Pre-market Approval (PMA) of its Isolex 300SA System.[8] In addition to effectively licensing and developing the technology, Hopkins, BD and Baxter have aggressively defended the patents in court. In 1994, the three parties joined in a suit against CellPro for infringement of the Civin patents.

Accordingly, NIH concludes that Hopkins and Baxter have taken effective steps to achieve practical application, as demonstrated by Hopkins' licensing, Baxter's manufacture, practice, and operation of the Isolex 300, and the device's availability to and use by the public to the extent permitted at this time under applicable law (i.e., foreign sales as well as widespread clinical research use in the U.S.). With regard to FDA approval and commercial sale of the Baxter Isolex 300 in the United States, the administrative record indicates that Baxter is vigorously pursuing an active application. Based on these facts, we conclude that Hopkins and Baxter have met the statutory and regulatory standard for practical application.

Health or Safety Needs

The question of whether the CellPro Ceprate SC fulfills health or safety needs not reasonably satisfied by the Baxter Isolex 300 has been the central inquiry and priority of the NIH in evaluating CellPro's petition for march-in. In this regard, we note the considerable debate among scientists and clinicians as to whether immunoselection of stem cells with selection devices prior to transplantation provides a clinically significant benefit to patients over standard hematopoietic

---

[8] CellPro has argued that the NIH should distinguish between the Isolex SA, an earlier, less automated device, and the Isolex 300i, Baxter's current fully-automated device. The current PMA application to FDA relates to the Isolex SA device. As is customary, the FDA recently discussed the Baxter PMA application for the 300SA device with the Biological Response Modifiers Advisory Committee (July 24, 1997). The majority of the committee members (13 out of 16) voted that the SA device yields an enriched cell population that produces successful engraftments. Thus, NIH finds that the Isolex SA and the 300i have comparable functions for the purpose of this determination.

transplantation techniques. The clinical benefit upon which the CellPro Ceprate SC device was approved by FDA consisted of a reduction of infusional toxicity associated with the administration of bone marrow prepared with standard techniques.[9] To date, neither party has presented to the Biological Response Modifiers Advisory Committee any studies documenting that cell separation devices improve stem cell engraftment, disease-free survival, or overall survival.[10] Thus, it is premature for either Baxter or CellPro to claim patient benefits (other than a decrease in infusional toxicities) from stem cell isolation and purification, T-cell, lymphocyte, and tumor cell purging, or other claimed uses.

It is equally premature, and inappropriate, for NIH to substitute its judgment for that of clinicians and patients seeking to avail themselves of an FDA-approved medical device. The FDA has determined that the Ceprate SC is safe and effective for selecting stem cells from autologous bone marrow for hematopoietic reconstitution. Thus, to the extent that the Ceprate SC is the only device that is available for sale in the United States for this purpose, it fulfills a health need for those who wish to use it, until such time as a comparable alternative product becomes available for sale.[11]

As explained more fully below, the administrative record demonstrates that Hopkins and Baxter have taken appropriate steps to reasonably satisfy this need. First, they have refrained from enforcing patent rights to the full extent of the law in order to allow the continuing sale of the Ceprate SC until the Baxter product is approved for sale by the FDA. Second, they have pledged to ensure that the Baxter product is as widely available as possible through clinical trials, and to ensure patient access to the fullest extent possible.

(1) Continuing Sale of CellPro Device

In deference to the health need fulfilled by the CellPro device in the absence of an FDA-approved

---

[9] See, Transcript, FDA Biological Response Modifiers Advisory Committee meeting, February 28, 1996; Package Description, Ceprate SC Stem Cell Concentration System (December 6, 1996).

[10] Transcript, FDA Biological Response Modifiers Advisory Committee meeting, February 28, 1996. At that public meeting, Dr. Richard Champlin, MD Anderson Cancer Center, introducing the CellPro device on behalf of CellPro, stated to the Committee, "[a]gain, one has to remember this is not a treatment for cancer. This is a means to enrich stem cells for a variety of purposes. It has again been shown to be reproducible, safe, and effective for that purpose. And this technology is really critical to allow us to develop the field in a number of other very important applications." Transcript at pp. 21-22.

[11] The Baxter Isolex 300 constitutes such a comparable alternative product. Both the Isolex 300 and the Ceprate SC devices are used in clinical research to isolate and purify stem cells from either bone marrow or peripheral blood, in preparation for stem cell transplantation. Both are under investigation for either autologous (patient's own) or allogeneic (donor) transplantations. We find that performance differences alleged by both parties primarily affect convenience of use, and do not alter the public health impact at issue here.

alternative, Hopkins and Baxter have refrained from enforcing their patent rights to the full extent of the law. Specifically, they modified a proposed order of injunction filed for consideration in the patent litigation in Federal District Court. The Order issued by the Court on July 24, 1997 states, in pertinent part:

> CellPro may continue to make, have made, use and sell SC Systems and disposable products (including the 12.8 antibody) for use with SC Systems, within the United States, until such time as an alternative stem cell concentration device, manufactured under a license under the '204 and '680 patents, is approved for therapeutic use in the United States by the United States Food and Drug Administration . . . and for a period of three months thereafter.

Order at p 5. In addition, certain price and volume restrictions contained in the Court's Order specifically do not apply to the provision of products solely for use in clinical trials. Order at pp. 5, 7.

CellPro argues vigorously, however, in documents filed prior to the entry of the Court's Order, that the terms of the proposed order, most specifically the requirement of payments to Baxter for sales of CellPro product, would force CellPro out of business and result in the loss of availability of the CellPro device.

First, we rely on the Court's finding that it is unlikely that the terms of the Order will result in the loss of availability of the CellPro product.[12] This issue was specifically before the Court, supported by an exhaustive factual record resulting from years of litigation. Although NIH is determining whether to open a fact-finding proceeding, as opposed to conducting one, we also found no convincing evidence that CellPro will be unable to supply patients with its product under the terms of the Court Order. The terms of the Order may be unpalatable to CellPro, but CellPro need only operate under those constraints pending a decision on its appeal of the Court's adverse verdict on infringement. The Court specifically found that CellPro "possesses adequate cash reserves to allow it to continue operations during the pendency of its appeal," Memorandum Opinion at p. 24, and determined that it would most likely be in CellPro's interest to continue operations pending the outcome of the appeal. Moreover, the Court has retained jurisdiction and invited the parties to apply to the Court for modification of the terms of the injunction, specifically, the payment of incremental profits to Baxter, if the amount determined by the Court "either provides inadequate relief or works an injustice inconsistent with equitable principles." Id.

---

[12] According to the Court in its Memorandum Opinion at p. 23, "[a]fter evaluating the parties' arguments, and their accompanying declarations, the court finds that in the absence of a conclusive statement from CellPro executives that it will discontinue operations, it has failed to establish that a highly speculative risk of shutdown during the pendency of its appeal to the Federal Circuit outweighs the harm suffered by plaintiffs as the result of CellPro's willful infringement." Nonetheless, the Court modified one of the terms of the injunction, as proposed by Hopkins and Baxter, to require CellPro to pay 60 percent of its incremental profit from infringing sales, as opposed to the 100 percent proposed by Hopkins and Baxter.

Second, the loss of availability of the CellPro product is relevant to the "health need" criteria only during the period prior to FDA approval and availability for sale of a comparable alternative product. In petitioning NIH to open a separate proceeding on this matter, CellPro argues that its continuing viability and success, even beyond FDA approval of a comparable alternative, should be a matter of concern to the NIH because CellPro has developed and is marketing an important health care product. Invoking our prior caveat as to the investigational nature of these devices, we concur that, as a general matter, NIH supports the development and success of the biotechnology industry. It is indeed very important to the NIH that biotechnology and pharmaceutical companies thrive and compete in order to bring new health care products to the public. Developing and commercializing such products out of federally-funded research is the foundation and essence of the Bayh-Dole Act.

We are wary, however, of forced attempts to influence the marketplace for the benefit of a single company, particularly when such actions may have far-reaching repercussions on many companies' and investors' future willingness to invest in federally funded medical technologies. The patent system, with its resultant predictability for investment and commercial development, is the means chosen by Congress for ensuring the development and dissemination of new and useful technologies. It has proven to be an effective means for the development of health care technologies. In exercising its authorities under the Bayh-Dole Act, NIH is mindful of the broader public health implications of a march-in proceeding, including the potential loss of new health care products yet to be developed from federally funded research.

On balance, we believe it is inappropriate for the NIH to intercede in this matter to ensure CellPro's commercial future. Viability and success in the private sector is appropriately governed by the marketplace, and significantly influenced by management practices and decisions. CellPro had the opportunity to license the invention from Baxter but decided against doing so, and instead risked patent infringement litigation. It would be inappropriate for the NIH, a public health agency, to exercise its authorities under the Bayh-Dole Act to procure for CellPro more favorable commercial terms than it can otherwise obtain from the Court or from the patent owners. CellPro's commercial viability is best left to CellPro's management and the marketplace.

(2) Reasonable Steps to Ensure Widespread Availability of Baxter's Product

Hopkins and Baxter have also pledged to reasonably satisfy any health need created by the loss of the CellPro product in the unlikely event that patient access to this technology is restricted before a comparable alternative product is approved by the FDA and becomes available for sale.

In several of its submissions to NIH, and in a letter from Baxter CEO Vernon Loucks to Secretary Donna Shalala, Baxter committed to ensuring there would be no gap in patient access to stem cell separation technology. Baxter committed to installing its device free of charge at any site from which CellPro might withdraw, and to provide that site with the same level of support on the same terms as CellPro. Baxter also committed to obtaining all clinical and regulatory approvals necessary to place the Isolex system into operation as soon as possible.

CellPro asserted that Baxter is unable to fulfill this pledge; however, neither party submitted evidence sufficient for a definitive determination, and it would be premature for the NIH to act

based on Baxter's failure to accomplish what events have not yet required it to do. In any event, we believe the likelihood of Baxter having to substitute devices in order to ensure patient access is remote, as discussed above. Nevertheless, pending FDA approval and availability for sale of a comparable alternative product, NIH will continue to monitor the situation and will retain jurisdiction to initiate march-in without the filing of a new request, in the event that health needs are not being reasonably satisfied.

Conclusion

The NIH has determined not to initiate proceedings to pursue march-in rights on the basis of the available information. NIH has examined the criteria of 35 U.S.C. § 203(1)(a) and (b) and found that march-in is not warranted under either criteria. Specifically, the NIH has determined that Hopkins and Baxter have taken, or are expected to take within a reasonable time, effective steps to achieve practical application of the applicable patents, as demonstrated by Hopkins' licensing activities and Baxter's manufacture, practice, and operation of the Isolex 300, as well as the pending applications for FDA approval. NIH also finds that the available information fails to demonstrate an unmet health need that is not reasonably satisfied by Hopkins and Baxter.

The NIH will continue to monitor issues related to patient access to the CellPro or Baxter devices during the period prior to FDA approval and availability for sale of a comparable alternative device.

Harold Varmus, M.D.
Director, NIH

AUG - 1 1997