MEMORANDUM

TO: Robert Lanman
NIH Legal Advisor

FROM: Lloyd Cutler
Wilmer, Cutler & Pickering

Birch Bayh
Bayh & Connaughton, P.C.

RE: Petition of CellPro, Inc. Requesting Exercise of March-In Rights

DATE: April 24, 1997

You have asked us in general to provide you with additional information regarding the statutory basis for granting CellPro's Petition of March 3, 1997, requesting that the Department of Health and Human Services exercise the government's march-in rights under the Bayh-Dole Act, 35 U.S.C. §200 et seq., to ensure that CellPro's CEPRATE SC Stem Cell Concentration System ("CEPRATE System") will remain available for use in stem cell transplants. In particular, you asked for further information about (1) the impact on the public health if sales of CellPro's CEPRATE System were enjoined as Baxter has recently requested and (2) the time and procedure that would be involved in Baxter's seeking FDA approval of a potentially competitive product. As discussed more fully below, the statutory criteria are plainly met, and the Department should act forthwith either to require Johns Hopkins to issue any required license or to issue the license itself.

I. INTRODUCTION AND SUMMARY

As anticipated in our March 3, 1997, Petition on behalf of CellPro, Baxter and the other plaintiffs in the ongoing patent litigation against CellPro filed on April 7, 1997, a motion seeking a permanent injunction against further sales of the CEPRATE System based on the Court's prior determinations that CellPro's use of the 12.8 antibody infringes the Civin patents assigned to Johns Hopkins and ultimately licensed to Baxter.[1/] The proposed injunction goes so far as to ask that CellPro be required to destroy not only existing stocks of the 12.8 antibody but also its hybridoma cell line used to produce the antibody -- a unique cell line that was discovered by researchers supported by NIH funding at the Fred Hutchinson Cancer Center and developed before the patents even issued. Perhaps one should not be surprised that a multi-billion dollar medical products company such as Baxter would seek such an injunction, notwithstanding that the only claim that has been or could be made against CellPro is that it is using technology that falls within a patent issued as a result of taxpayer-funded research at Johns Hopkins, of which Baxter is now the beneficiary. And while (no doubt to try to convince the Department that there is no need for the exercise of its march-in rights) Baxter includes in its proposed injunction a partial stay that would permit limited sales of the disposable column and antibody kits necessary to use the CEPRATE System, the terms of the proposed stay would severely limit the number of patients who could benefit from the FDA approved product and require that Baxter be paid a royalty of approximately 50% of the sales price while CellPro would incur a substantial and unsustainable loss on each sale. It is unclear whether CellPro or any company could, or whether

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[1/] Baxter's Motion for Entry of Permanent Injunction and Brief in Support of Plaintiffs' Motion for Permanent Injunction are provided in Exhibit Volume I, Tab 1.

any rational enterprise would, continue to supply a product on such terms, even during the period of an appeal of the adverse judgement in the patent case. But even if it could, the terms of the injunction proposed by Baxter do not come close to satisfying the public health need. CellPro has opposed Baxter's motion for injunctive relief on a variety of grounds, prominent among them that it would not be in the public interest.[2/] In support of its opposition, CellPro submitted the declarations of 26 doctors who are using the CEPRATE System to treat patients and conduct clinical studies outlining various ways in which the injunction proposed by Baxter would adversely affect their patients and their work [3/].

Baxter proposes that no new sales or other transfers of the CEPRATE System be permitted. Baxter does propose that, pending FDA approval of another product licensed under the Johns Hopkins patents, CellPro be allowed (on the unprofitable terms noted above) to continue selling disposable columns and antibodies to hospitals and other facilities that had purchased the CEPRATE System prior to March 12, 1997. Baxter plainly recognizes that the public health need precludes simply forcing the CellPro product off the market as it previously threatened to try to do. But even on Baxter's proposed terms, it is apparent that thousands of victims of the most acute forms of metastatic breast cancer -- the disease that was the subject of the clinical trials that led to FDA approval of the CEPRATE System -- would be forced to

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[2/] See CellPro's Brief in Opposition to Plaintiff's Motion for a Permanent Injunction and in Support of Alternative Motion for Stay of Injunction Pending Appeal (Exhibit Volume I, Tab 2).

[3/] Copies of these declarations (including the first page of the declarant's curriculum vitae, complete copies of which can be provided on request) are included in Exhibit Volume II at Tabs A-Z, and a number of them are cited with regard to specific discussions below.

undergo less optimal treatment with unnecessary suffering and in some cases death while Baxter's FDA application is in process, without any present assurance that the FDA will approve Baxter's product or that the product will be as safe and effective as CellPro's. The same is true of victims of lymphoma, multiple myeloma, neuroblastoma, leukemia, and other cancers that would benefit from the FDA's approval of the CEPRATE System.

Moreover, there are numerous ongoing clinical trials -- some of which are being conducted by NIH itself, others with substantial NIH funding – involving stem cell separation using the CEPRATE System alone or in combination with additional second generation, novel systems. Because the proposed injunction would require that all sales of columns and antibodies be made at full price, these ongoing trials and others planned for the immediate future, which depend on a free supply of columns and antibodies, would have to be discontinued. This would mean not only that efforts to gain approval for new applications of the CEPRATE System would have to be discontinued but also that the development of second generation products would be completely terminated. The inevitable result would be to curtail advances in the treatment of some of the most grave forms of cancer and of other, as yet, non-curable diseases such as severe autoimmunity and HIV.

Perhaps most significant is the ongoing phase I/II clinical trial involving transplants from parents to their children with leukemia. These children have failed standard therapy, can find no matched donor, and have no option other than a parent to serve as a stem cell donor for a potentially life-saving transplant. This study involves use of both the CEPRATE System and a second generation CellPro product designed to expand the availability of bone

marrow transplants to patients for whom no matching donor can be found. Unless these children can participate in this study, they will surely die.

Clinical trials using other second generation products that work with the CEPRATE System are scheduled to begin this year. One promising application involves using the CEPRATE System to reduce the likelihood of cancer recurrence from the reintroduction of tumor cells in the course of bone marrow transplants. But it is not only cancer patients who will suffer if the CEPRATE System is unavailable. Since FDA approval, investigators have proposed new studies using the CEPRATE System for the treatment of patients with autoimmune diseases such as multiple sclerosis, infectious diseases such as AIDS, and a variety of genetic diseases. Unless the Department acts, all of this work would be subject to the proposed Baxter injunction and would have to cease with the effect of delaying indefinitely new FDA approvals and the development of promising new treatments.

The consequences in terms of the untold suffering if not death of thousands of children and adults cannot be justified as a way to ensure that there will be a market for Baxter's own product, if and when FDA approval can be obtained. CellPro does not have access to much of the information that would be necessary to say just where in the regulatory approval process Baxter's February 24, 1997, application for pre-market approval (PMA) of its Isolex stem cell separation product stands, whether that application will eventually prove successful, or how long it will take before it can be known whether FDA approval will be forthcoming or not. Based on the information that is available, however, there is no reason to believe that Baxter's application could be processed in less than the average time for consideration of such requests, which is

more than two years from the filing of an acceptable application. In fact, Baxter's application would appear to be supported by data that is both incomplete and based at least in part on clinical trials of an earlier product using different technology. Because of serious questions concerning the safety and efficacy of both Baxter's earlier generation products and its current device, CellPro would expect the FDA to require a new prospective, randomized phase III clinical trial with primary safety and efficacy endpoints agreed to by the FDA of the type CellPro was required to conduct before its PMA application was accepted. Based on CellPro's experience (which consumed almost seven years, including three years after its PMA application was accepted), CellPro would expect that enrollment, testing, and evaluation for such a clinical trial would take a minimum of a year for accrual and appropriate follow-up, 6 months to audit, collect, and analyze the data, and a minimum of two additional years before approval could be granted if the clinical trial proves successful.

For Baxter, whatever time it takes – and whatever the consequences to cancer victims and others who are denied the beneficial aspects of the CEPRATE System – can be justified to protect "the public interest in maintaining the integrity of the patent system."[4] But whatever justifications might exist for such a position in the case of a patent that resulted from private investment, they have no application whatever in the present circumstances. For here both the Johns Hopkins patents and the antibody used by CellPro that has been found to infringe were the products of separate taxpayer-funded research. When Baxter took a license to the Johns Hopkins patents – a license to which CellPro should have had a statutory preference in the first

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[4] Brief in Support of Plaintiffs' Motion for a Permanent Injunction at 2 (Exhibit Volume I, Tab 1).

place -- Baxter was on full notice that the government retained its Bayh-Dole march-in rights in the invention as a result of the funding it had provided.[5] As discussed below, not only was there an inordinate delay by Johns Hopkins and its licensees in attempting to develop a product for therapeutic uses, but there are a number of health needs that can only be served by CellPro's FDA-approved CEPRATE System. Any one of these health needs would more than satisfy the statutory criteria for exercise of the government's march-in rights. Together, they mandate the quickest possible action to protect the nation's health and ensure continued availability of an important new product that resulted from taxpayer investment.

II. THE STATUTORY CRITERIA

Under the Bayh-Dole Act, a federal agency may exercise its march-in rights upon a determination that:

> (a) action is necessary because the contractor or assignee has not taken, or is not expected to take in a reasonable time, effective steps to achieve practical application of the subject invention in such field of use; [or]
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> (b) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees.

Both of these criteria are readily met given Baxter's refusal, as discussed in the CellPro Petition, to issue a license on reasonable terms. The CEPRATE System has significantly improved the treatment of patients with various forms of cancer and provides a life-saving option for many patients who would otherwise die. Moreover, the second generation products to be used in

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[5] Not only do the patents expressly note the government's rights, but the license agreement by which Baxter obtained exclusive therapeutic rights expressly granted those rights subject to the requirements of the Bayh-Dole Act.

conjunction with the CEPRATE System offer the hope of treatment for many patients suffering from previously untreatable diseases. As discussed in greater detail below, the public health needs of the nation require that the government exercise its march-in rights to prevent Baxter from putting in jeopardy the health and lives of countless adults and children. As also discussed in detail below, Baxter has not taken and cannot be expected to take within a reasonable time effective steps to achieve the FDA approval that is necessary to the practical application of the Johns Hopkins patents so as to satisfy the health needs being currently served by the CEPRATE System.

III. PUBLIC HEALTH NEEDS

The CEPRATE System has been approved by the FDA for use in autologous bone marrow transplantation, a procedure used to treat patients with breast cancer, multiple myeloma, lymphoma, and other diseases. At the end of 1996, the CEPRATE System was in use at over 200 medical facilities around the world, including at the NIH.[6] Since its FDA approval in December 1996 (and despite the overhanging cloud caused by the ongoing patent litigation), more than 20 hospitals and transplant centers in the United States have acquired new or additional CEPRATE Systems, with new requests and inquiries coming in on almost a daily basis. CellPro believes that (assuming the government asserts its march-in rights to preclude the injunction being sought by Baxter) its product will be in use in facilities that perform 80-90%

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[6] See CellPro literature describing CEPRATE System (Exhibit Volume I, Tab 3). The CEPRATE System may be viewed in operation at the NIH Cell Processing Lab. For further information, contact Charlie Carter, NIH Department of Transplants, Medical Building - Cell Processing Lab, Building 10, Room 1C711, 10 Center Drive, Bethesda, Maryland 20892; (301) 496-0029.

percent of the country's bone marrow transplants by the end of 1997. Of the approximately 5000 patients in the United States, Canada, and Europe who were treated with the CEPRATE System through 1996, about 40% were treated for breast cancer, 25% each for lymphoma and multiple myeloma, and 10% for leukemia and various other diseases. For the next two or three years, this pattern of use is likely to expand and include other indications such as treatment of autoimmune diseases, HIV, genetic disorders, solid organ transplants, and *in utero* transplantation. For most of these categories of diseases there is a major health need that can only be satisfied by continued use of the CEPRATE System.

A. BREAST CANCER

Breast cancer is, of course, one of the country's major health problems. Each year, more than 180,000 women in this country are diagnosed with breast cancer. And notwithstanding improvements in detection and treatment, more than 44,000 women in the United States die from the disease each year. The CEPRATE System can substantially improve the treatment process for many women with the most advanced cases of the disease whose treatment involves high dose chemotherapy and autologous stem cell transplantation.

When women with breast cancer receive high dose chemotherapy, the result is to destroy not only cancer cells in the body but also the cells of the immune system, including stem cells which are the early-stage cells that generate and replace the other functional cells in our blood and immune systems. After treatment, a source of new stem cells must be administered as soon as possible to rebuild those systems for patients who in the meantime have no defense to infection and disease.

In the past, bone marrow was the only source of stem cells available to patients who received high dose chemotherapy. Prior to the transplant, a portion of the patient's bone marrow was removed, then frozen for later use as a source of stem cells. More recently, it has been discovered that certain drugs can cause the bone marrow to release large numbers of stem cells into the blood stream, and those cells can then be isolated in the white cell fraction of the peripheral blood. Whether stem cells are obtained from bone marrow or peripheral blood, however, two major medical problems accompany autologous (using the patient's own cells) stem cell transplantation for the treatment of breast cancer and other diseases: adverse side effects associated with the transplant process and reinfusion of tumor cells that are present in the patient's bone marrow or circulating in the patient's peripheral blood. Use of the CellPro CEPRATE System serves a critical health need involving both of these problems.

1. Minimizing Serious Adverse Side Effects.

When bone marrow or peripheral blood is harvested and frozen for later transplantation following high-dose chemo and radiation therapy, cryoprotective agents are added to the white cell fraction before freezing to protect cell membranes. However, those agents are toxic and can cause serious and at times life threatening cardiovascular, renal, and other problems when the cryopreserved cells are reintroduced into the body.[7] Serious or life-threatening events after infusion of marrow have been reported to occur in 5 - 10% of

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[7] See, e.g., Declaration of Dr. Stanley Calderwood at 2-4 (Exhibit Volume II, Tab H); Declaration of Dr. Cesar O. Freytes at 2 (Exhibit Volume II, Tab L); Declaration of Dr. Kent Holland at 2-3 (Exhibit Volume II, Tab P); Declaration of Dr. Gary Schiller at 1 (Exhibit Volume II, Tab V).

patients who undergo traditional bone marrow transplantation.[9] CellPro's phase III study showed that use of the CEPRATE System to select stem cells eliminates this problem.

Use of the CEPRATE System involves harvesting stem cells from the patient's bone marrow or peripheral blood as in the case of traditional transplants.[9] Instead of freezing and transplanting the entire white cell fraction, however, that fraction is incubated with the 12.8 antibody discovered by researchers at the Fred Hutchinson Center. During the short incubation period, the antibody attaches itself to stem cells but generally does not attach itself to other cells. Next, the cells are passed through a continuous-flow column coated with avidin, a common protein. The antibodies are linked to a molecule of biotin, a vitamin that adheres to

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[9] There is substantial documentation of adverse side effects experienced by cancer patients undergoing bone marrow transplantation. For example, one study reported a patient with ovarian cancer who sustained a cardiac arrest immediately following autologous marrow infusion. Vriesendorp R, et al., Effective high-dose chemotherapy with autologous bone marrow infusion in resistant ovarian cancer, Gynecol Oncol 17:271 (1984). Another evaluated 33 consecutive patients undergoing autologous bone marrow transplantation. All of these patients developed hemoglobinuria, and three developed acute renal failure that was attributed to marrow infusion. These three patients died, showing acute renal tubular necrosis at autopsy. Smith DM, et al., Acute renal failure associated with autologous Bone Marrow Transplantation, Bone Marrow Transplantation, 2:195 (1987). A third study reported a patient with Hodgkin's disease who developed acute respiratory failure culminating in cardiac arrest immediately following infusion of autologous marrow. Rapoport AP, et al., Cardiac arrest after autologous marrow infusion, Bone Marrow Transplantation, 7:401-403 (1991).

[9] Although the FDA approval of the CEPRATE System was technically for use in bone marrow transplants, many doctors have found it equally if not more effective in "off label" transplants of stem cells from peripheral blood. Since the FDA regulates the sale and marketing of medical products and not the practice of medicine, physicians are free to use FDA-approved products for off-label applications. CellPro believes that peripheral blood is the source of stem cells in a majority of transplants performed today using the CEPRATE System and is moving rapidly to obtain FDA approval for this application. As discussed below, CellPro has completed a phase III clinical trial using peripheral blood and intends to request an expansion to its existing approval to include peripheral blood later this year.

avidin on the surface of the column. As the incubated white blood fraction flows through the column, the stem cells remain and the unwanted cells pass through and are washed away. The stem cells are then removed from the column by gentle agitation and are ready to be frozen for later transplant into the patient after she has undergone chemotherapy treatment. By its selective harvest of stem cells, the CEPRATE System greatly reduces the necessary volume of reinfused material, as well as the volume of required cryoprotective agent.

The Phase III breast cancer study conducted by CellPro and submitted in a PMA application to the FDA in December 1993 (BP-940001) demonstrated that use of the CEPRATE System substantially reduces cardiovascular and other toxicities associated with infusion of whole marrow. Only 16 grade III adverse events occurred in the 42 patients using the CEPRATE System as a result of the transplant, compared to 33 adverse events in the 47 patients in the control group who underwent traditional bone marrow transplantation. Moreover, three of the control group patients experienced serious adverse side effects whereas none of the patients treated using the CEPRATE System did so.

The serious adverse side effects (considered clinically significant) experienced by the control group patients included one patient who required endotracheal intubation after the start of the marrow infusion due to a significant decrease in oxygen saturation and who later died, with an autopsy showing pulmonary congestion. The patient had required oxygen prior to transplant due to chemotherapy related pulmonary toxicity, and the temporal association of the marrow infusion with the rapid deterioration of the patient's pulmonary status suggested that the infusion played a significant role in the patient's development of acute respiratory failure.

Another patient developed an anaphylactoid reaction consisting of acute bronchospasm with a concomitant decrease in oxygen saturation along with severe nausea, vomiting, and abdominal cramping fifteen minutes after the beginning of the infusion, and a third control group patient experienced transient renal failure.

The CEPRATE System not only eliminates these serious adverse side effects, it also helps reduce the need for medical interventions. The breast cancer patients treated with the CEPRATE System in CellPro's phase III study required only half the number of medical interventions required by the control group patients, and urgent medical interventions occurred exclusively in the control group.[10/]

CellPro estimates that over the next five years, approximately 50,000 women in the United States will undergo stem cell transplantation for the treatment of breast cancer. If it remains freely available, CellPro believes that the CEPRATE System will be used in the transplants of at least 40% of these women by the year 2000, thereby greatly reducing their suffering and discomfort from adverse events, reducing the need for medical intervention both during and immediately after treatment, and even reducing the risk of death as there is a reported one to two percent mortality (or between 10 and 20 deaths per 1,000 transplants) that results from the toxic agents that would otherwise be used during the treatment process itself. CellPro

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[10/] The urgent medical interventions experienced by the control group patients in CellPro's Phase III breast cancer study included one control group patient who required emergency endotracheal intubation and mechanical ventilatory support during the marrow infusion. Five patients required a decrease in their marrow infusion rate due to toxicities which included severe nausea and vomiting, headaches, an anaphylactoid reaction and acute respiratory failure. And four patients required additional intravenous fluids for gross hematuria.

is aware of no evidence that the Baxter system can accomplish a similar reduction of adverse events. Even if the Baxter product were to be approved by the FDA during the next two to three years, many women would in the meantime lose access to the benefits of the CEPRATE System because their doctors would not have available one of the limited number of systems sold in the United States before March 12, 1997. The only way to satisfy the health needs of these breast cancer patients is through the exercise of the government's march-in rights.

2. Depleting Tumor Cells.

A second major medical challenge associated with bone marrow transplantation is preventing relapse. The blood or bone marrow of many breast and other cancer patients contains tumor cells which, if returned to the patient, may contribute to relapse of the disease. Because of the scale of the study required and the length of time needed, it will be some time before there will be definitive information on whether the CEPRATE System in fact helps prevent relapse of breast or other cancers by removing tumor cells from the bone marrow or peripheral blood while selecting stem cells. Gene marking studies have, however, shown that tumor cells given back to patients in the transplant procedure can contribute to relapse of the disease. Shpall and her colleagues at the University of Colorado evaluated both bone marrow and peripheral blood samples from breast cancer patients for tumor cell contamination before and after selection with the CEPRATE System under the auspices of an NIH grant. They found tumor cells in the bone marrow of 13 of 25 patients and the peripheral blood of 3 of 18 patients prior to stem cell selection. After selection, there were no tumor cells in 5 of the 13 bone marrow samples and in

all three of the peripheral blood samples.[11/] What this data strongly suggests is that the depletion of tumor cells that occurs as a result of stem cell selection by the CEPRATE System may contribute to preventing relapse and improving the survival rate of women who suffer from breast cancer.

Moreover, CellPro is working on a second generation product, combining the CEPRATE System with a monoclonal antibody-based breast cancer purging column designed to purge even more tumor cells than are depleted using the CEPRATE System alone. CellPro expects that use of this product in which white cell fractions from bone marrow or peripheral blood will be passed through both the CEPRATE column and the tumor cell depletion column will enable transplantation with extremely low numbers of tumor cells, even below the level of detection. Clinical trials are in the planning stage for this new product which has the possibility of saving even more lives of breast cancer patients -- trials that would have to be terminated if Baxter were to succeed in removing the CellPro product from the market notwithstanding the clear health need in this area.

11/ As discussed below, other researchers have obtained similar results in the treatment of other malignancies. See, e.g., Declaration of Dr. Kenneth Anderson at 2 (Exhibit Volume II, Tab B); Statement of Dr. Anthony Elias at 1 (Exhibit Volume II, Tab K). Dr. Elias is currently conducting a clinical trial, in part funded by the NIH, for the treatment of small cell lung cancer. He has found that "[p]rocessing of the peripheral blood with the CEPRATE SC System results in substantial reduction in tumor contamination." For example, in one patient tumor contamination was reduced from 170 cells per million to zero. In addition, of the 14 patients he has treated to date (out of 30 planned) only 2 patients have relapsed. See also Summary of Results from Published Studies Using the CEPRATE SC Stem Cell Concentration System for Depletion of Tumor Cells in Peripheral Blood and Bone Marrow (Exhibit Volume I, Tab 4).

B. LYMPHOMA AND MULTIPLE MYELOMA

In addition to its use in the treatment of breast cancer, CellPro's CEPRATE System has been used extensively in the treatment of patients with lymphoma and multiple myeloma. Each year in this country over 45,000 patients are diagnosed with lymphoma, and over 13,000 patients are diagnosed with multiple myeloma. In the past, many of these patients were treated with traditional bone marrow transplantation and experienced the same side effects suffered by breast cancer patients. Just as the CEPRATE System has been used successfully in the treatment of breast cancer to reduce the risk of serious side effects and possible death, it can also be used for these purposes in the treatment of lymphoma and multiple myeloma. Worldwide, approximately 1,200 lymphoma and 1,200 multiple myeloma patients have been successfully treated using the CEPRATE System. As in the case of breast cancer, the injunction sought by Baxter would have a serious, adverse impact on the expanded treatment of lymphoma and multiple myeloma patients.

In this regard, several studies have shown that the existence of tumor cells in bone marrow or peripheral blood prior to reinfusion is directly related to the likelihood of relapse in lymphoma and multiple myeloma patients. Gribben and his collaborators at Dana Farber Cancer Institute and Harvard University Medical School used PCR to detect lymphoma cells in bone marrow before and after purging in 114 patients with B-cell non-Hodgkins lymphoma. Disease-free survival was significantly increased in the patients whose marrow infusion at the time of transplant did not contain detectable lymphoma cells compared to those patients with residual, detectable lymphoma cells in the marrow infusion. Similar results were obtained by Sharp and

his collaborators at the University of Nebraska using a culture technique sensitive for detecting occult non-Hodgkins lymphoma cells in bone marrow. In a group of 24 patients, the bone marrow infused was culture positive in eleven patients and culture negative in 13 patients. The survival at three years for the culture positive patients was 5.5%, while in the culture negative patients it was 35.7%.

Because of this evidence and other research referred to above, efforts have been made to find ways to purge tumor cells before transplantation. CellPro has recently concluded a Phase III clinical study with the primary efficacy endpoint of tumor purging using the CEPRATE System, as agreed upon by FDA, from the graft of multiple myeloma patients. CellPro presently anticipates filing a supplemental PMA application later this year based on this phase III clinical trial and that it will be successful in obtaining FDA approval for use of the CEPRATE System for tumor cell reduction in cancer patients receiving bone marrow or peripheral blood transplants. Once that approval is obtained -- absent the prohibition on additional sales of the System being sought by Baxter -- it is likely that an even higher percentage of patients will benefit from the use of the CEPRATE System than in the past.

Moreover, CellPro is working on another second generation product to be used in combination with the CEPRATE System designed to purge additional tumor cells from the graft of lymphoma patients. This device has already been used successfully to treat two lymphoma patients, including Rick Murdock, the President of CellPro, under compassionate use applications. Treatment with the CEPRATE System and the tumor cell depletion column completely eradicated the presence of tumor cells from the patients' marrow and peripheral

blood. Clinical trials for the tumor cell depletion column are scheduled to begin in the near future. Despite evidence that numerous lymphoma patients could benefit from treatment with this product, all of these trials would have to be discontinued if Baxter's injunction were granted.

C. LEUKEMIA

Patients with certain diseases, such as leukemia, cannot use their own stem cells for transplantation because those cells may themselves carry the disease. For leukemia patients, the preferred treatment often involves an allogeneic transplant, meaning that the bone marrow or peripheral blood comes not from the patient but rather from a donor, usually a brother or sister who is genetically "matched" to the patient. In the allogeneic setting, tumor contamination is not a concern, but T-cells in the graft which can cause graft versus host disease (GVHD) are. T-cells are immune system cells that circulate in the blood. Following allogeneic transplantation T-cells can activate and attack the recipient patient's own normal cells causing GVHD which often leads to death. Transplants of unmodified bone marrow from genetically mismatched related donors have been associated with a high risk of severe acute GVHD (60-70%) and graft failure (24%).[12/]

One area where there is a large demand for allogeneic transplantation is in the treatment of leukemia in children. Over 2,000 children in this country are diagnosed with leukemia each year. For children who do not respond to standard treatment, allogeneic transplantation is often the treatment of choice. Unfortunately, fewer than one-third of the

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12/ See Beatty PG, et al., Marrow Transplantation From Related Donors Other Than HLA-Identical Siblings, N.Engl.J.Med. 313, 765-771 (1985).

children who might benefit from an allogeneic transplant have a genetically matched sibling available to serve as a donor. Approximately 50 percent of Caucasian children in North America who lack a genetically matched sibling will find a suitable genetically matched unrelated donor in the unrelated bone marrow donor registries. Non-Caucasian children or children with mixed racial and ethnic backgrounds, however, are much less likely to find a suitably matched unrelated donor.[13/] In addition, even where a match may eventually be found, the time required to initiate an unrelated donor search, screen the donors, procure the marrow, and initiate the transplant is four months on average and can be longer. In many children with leukemia who need a transplant, this is too long.

Until recently, children for whom no matched donor could be found had no chance of survival. The CEPRATE System, however, has provided hope for them.[14/] Partially-matched, related donors (parents or siblings) are available to most patients, and results of ongoing clinical trials indicate that the CEPRATE System can be used successfully to deplete the presence of T-cells in the graft and thereby permit donation from parent to child. Cottler-Fox and other scientists at the NIH calculated the amount of T-cell depletion obtained in bone marrow and peripheral blood by treating a group of 11 patients with the CEPRATE System. They concluded that the CEPRATE System depleted the number of T-cells by a mean of 3 logs from the starting number while concentrating stem cells. Another study conducted by Link and

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[13/] See, e.g., Declaration of Dr. John DiPersio at 1 (Exhibit Volume II, Tab J).

[14/] See, e.g., Declaration of Dr. Claudio Anasetti at 2 (Exhibit Volume II, Tab A); Declaration of Dr. Richard Burt at 5 (Exhibit Volume II, Tab G); Declaration of Dr. Fred LeMaistre at 3 (Exhibit Volume II, Tab R). See also Keith Ervin, Patent Litigation Threatens Cell-Therapy Progress, Seattle Times, April 17, 1997 (Exhibit Volume I, Tab 5).

his colleagues from the Blood Bank and the Department of Immunohematology/Transfusion Medicine at the Medical School in Hanover reported that processing with the CEPRATE System decreased the number of T-cells in the graft of 20 patients by more than 1000 fold while still maintaining high numbers of stem cells. Similar results have been reported by physicians at the University of California at Los Angeles and the Fred Hutchinson Cancer Research Center as well as other major research institutions.[15] In addition, children with leukemia have been treated using the CEPRATE System in CellPro-sponsored clinical trials at several U.S. cancer research hospitals. Without transplantation, these children had no more than 3 to 6 months to live. Statistical analysis was performed on the children who participated in the most recent of these trials indicating a 45% survival rate -- compared to the 100% mortality rate that was otherwise expected.[16]

A further important benefit of the CEPRATE System is the recent evidence of a dramatic reduction in the length of the engraftment period when the product is used in allogeneic transplants. The time period between myeloablation (i.e., the eradication of the patient's bone marrow and, with it, his or her ability to make blood and immune-system cells) and engraftment (which marks the restoration of hematopoiesis, the body's ability to make blood and immune-system cells) is a time period during which the patient is without a functioning immune system. During that time period the patient is at grave peril of death from opportunistic infections. The

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[15] See Summary of the Data Reported on Depletion of T-Cells from Bone Marrow and Peripheral Blood after Selection with the CEPRATE SC (Exhibit Volume I, Tab 6).

[16] See, e.g., Declaration of Dr. Kent Holland at 6 (Exhibit Volume II, Tab P); Declaration of Dr. Andrew Yeager at 1-3 (Exhibit Volume II, Tab Y).

CEPRATE System has been found to reduce this period of extreme vulnerability from 18-21 days to 8 days.[17] This dramatically reduces the patient's exposure to life-threatening infections. In addition, by reducing the patient's hospital stay from 30 to 11 days, the CEPRATE System provides great cost savings to the patient (and the health care system).

The foregoing studies alone make clear that the existing CEPRATE System has great potential in terms of significant advances in the treatment of leukemia. Moreover, in order to address the need for additional T-cell depletion in the mismatched setting to prevent GVHD in allogeneic transplant patients, CellPro has developed another second generation product, the CEPRATE TCD T-Cell Depletion System (the "TCD System") to further deplete T-Cells from the graft. A Phase I/II clinical trial using the TCD System began earlier this year. The trial is scheduled to enroll approximately 25 children with leukemia who need a stem cell transplant, but have no genetically-matched siblings to serve as a donor or for whom no phenotypically-matched unrelated donor can be found. The children in this trial will instead receive peripheral blood cell transplants from a family member (usually a parent) who is only partially genetically-matched. The peripheral blood cells will be processed using the CEPRATE and TCD Systems to first concentrate the stem cells and then reduce the number of T-lymphocytes. If proven to be safe and effective, use of the TCD System could further revolutionize allogeneic transplantation by making the process even safer and providing more viable treatment options for many patients, such as the children in the clinical trial, who are unable to locate a compatible donor. Even the threat that the CEPRATE System might have to be removed from the market is having a chilling

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[17] See, e.g., Declaration of Dr. Richard Burt at 2 (Exhibit Volume II, Tab G).

effect on researchers, and any actual removal of the product from the market threatens a life-saving treatment option for thousands of children and adults who have leukemia or who will develop it and who will die unless the ongoing research is allowed to continue.[18]

D. OTHER APPLICATIONS

Other applications for the CEPRATE System currently involved in clinical trials or other research include the treatment of autoimmune diseases, HIV therapy, solid organ transplantation, and gene therapy. CellPro has received numerous requests from investigators throughout the United States to perform clinical studies using the CEPRATE System for these and other applications, and the number of requests has increased substantially since the FDA approval finding the product safe and effective in selecting stem cells for transplantation. At the time FDA approved the product, there were 60 ongoing, investigator-sponsored studies using the CEPRATE System.[19] Some of the treatment applications they are studying – many, if not all, of

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[18] See, e.g., Declaration of Dr. Andrew Yeager at 3 (Exhibit Volume II, Tab Y).

[19] A complete list of these studies is provided in Exhibit Volume I, Tab 7. As a direct outcome of these clinical studies, there are more than 300 publications and abstracts of reports using the CEPRATE System including 45 publications reporting on research sponsored by NIH/NCI funding. A list of published studies is included in Exhibit Volume I, Tab 8. A list of published studies supported by NIH/NCI funding is provided in Exhibit Volume I, Tab 9. Copies of these studies can be provided on request. A separate list of abstracts from the American Society of Hematology meeting in December 1996, at the time of CellPro's PMA approval, is included in Exhibit Volume I, Tab 10.

which would come to a halt under the terms of the injunction proposed by Baxter[20/] -- are discussed briefly below.

Multiple Sclerosis and Other Autoimmune Diseases. Diseases such as multiple sclerosis, lupus, and rheumatoid arthritis are caused by the patient's own immune cells attacking normal tissues. Nationwide, more than 3 million patients suffer from these diseases and over 500,000 of those are severe cases that could potentially benefit from treatment with the CEPRATE System. It has been observed that a number of cancer patients with co-existing autoimmune disease have experienced some improvement of their autoimmune conditions following stem cell transplantation as part of their cancer treatment. This has led to a strong interest in using high-dose chemotherapy and autologous transplantation as therapy for this serious and debilitating group of diseases. The first trial involving the use of the CEPRATE System for treatment of autoimmune disease has recently begun at Northwestern University and the University of Wisconsin. The first patients to receive the treatment suffered from multiple sclerosis. Although the cause of the disease is not known, it is believed that powerful immune suppression (myeloablative chemotherapy) followed by stem cell support may reestablish a normal immune system. Submitted herewith is a videotape of news reports carried in the Chicago area following the test which provides compelling evidence of the need to support and continue research in this area.

20/ See, e.g., Declaration of Dr. Edward Ball at 2 (stating that he would have to discontinue his clinical trial for the treatment of Gaucher disease) (Exhibit Volume II, Tab C); Declaration of Dr. John Zaia at 4 (stating that he would have to discontinue his clinical trial for the treatment of AIDS) (Exhibit Volume II, Tab Z).

HIV. Recent studies using the CEPRATE System have shown that stem cells selected from HIV-1 infected patients are free from viral infection, making them suitable for use in stem cell transplantation and immune system reconstitution after destruction of the patient's infected T-cells by chemotherapy or radiation. Another clinical study is currently planned to investigate the efficacy of transplanting genetically modified stem cells to treat HIV. In this study, the CEPRATE System will be used to select stem cells from HIV-infected patients. A gene will be inserted into the stem cells and the modified cells will be given back to the patient. The intended result of the trial is that the genetically modified cells will produce T-cells that are resistant to HIV infection. If successful, this trial could represent a major step toward successful gene therapy treatments for HIV and other diseases.

Solid Organ Transplantation. Transplantation of organs such as the liver, kidney, and heart, while clinically effective, often require life-long and potentially harmful immunosuppression to prevent rejection of the transplanted organ. Researchers have attempted to reduce or eliminate the need for this immunosuppression by inducing tolerance to the transplanted organ. One method involves administering stem cells from the organ donor to the transplant recipient. These donor stem cells interact with the recipient's immune system to create tolerance. Researchers are using the CEPRATE System to select the stem cells while depleting the donor T-cells that could cause GVHD in the transplant recipient. Clinical trials using the CEPRATE System have already begun in Europe, and additional trials are scheduled in the U.S. later this year.

Gene Therapy. Gene therapy could potentially cure many diseases such as Thalassemia, Sickle Cell, Gaucher's, and Severe Combined Immunodeficiency (SCID).[21] Gene therapy could also enhance treatment options for cancer and infectious diseases like AIDS. Stem cells are ideal targets for genetic modification because they can be transplanted, they can divide to make more of themselves, and they can generate large numbers of all the mature blood cell types. Enrichment of the stem cells prior to the genetic modification is critical for economies of scale as well as to improve the efficiency of genetic transfer. A sample of concentrated stem cells requires significantly less of the expensive and relatively scarce materials used to transfer genes into cells (retroviral supernatant, culture media, and recombinant cytokines) as compared to unprocessed bone marrow or peripheral blood.

Currently, the CEPRATE System has been incorporated into over 20 different clinical gene therapy protocols, with some 150 patients treated at leading academic institutions such as the NIH, MD Anderson, FHCRC, University of Pittsburgh, Columbia, and Children's Hospital in Los Angeles. These studies have included gene marking to examine the contribution of reinfused cells to disease relapse, therapeutic studies to insert the ADA or GC genes into patients with either SCID or Gaucher's, as well as transduction of the MDR gene to enhance

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[21] An article in the December 12, 1996, edition of the New England Journal of Medicine included in Exhibit Volume I, Tab 11, described the use of an allogeneic transplant to treat a four month old fetus diagnosed as having SCIDS, a fatal condition in which patients fail to make functional immune cells and thus cannot ward off even minor infections. CellPro's CEPRATE System was used to purify stem cells from the baby's father, which were then administered to the fetus *in utero*. After 18 months of age, the child showed no sign of his life-threatening illness. Other independent investigators are currently using the CEPRATE System in several additional *in utero* transplant studies.

chemotherapy resistance in breast and ovarian cancer patients.[22] All of these studies have shown that stem cells, enriched with the CEPRATE System, can achieve transfer of the gene into the cell, can safely be used to reconstitute the patient's blood and immune systems, and can show long-term persistence of those genetically marked cells.

* * * *

In sum, the CEPRATE System, by making stem cell transplantation a viable and effective treatment option for victims of breast cancer, lymphoma, multiple myeloma, leukemia and other cancers, fulfills a vital public health need.[23] In addition, preliminary results from numerous ongoing research and clinical trials indicate that the CEPRATE System and second generation products to be used in conjunction with the CEPRATE System offer the hope of new treatment options for victims of other as yet, non-curable diseases such as severe autoimmunity and HIV.[24] These urgent public health needs provide compelling grounds for the Department of Health and Human Services to exercise its march-in rights pursuant to the Bayh-Dole Act and require Johns Hopkins to issue a license to CellPro on reasonable terms.

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[22] See, e.g., Declaration of Dr. Fred LeMaistre at 4 (Exhibit Volume II, Tab R).

[23] Id. at 5.

[24] Id. at 6-8.

IV. EFFORTS OF THE GRANTEE AND ITS LICENSEES TO UTILIZE THE PATENTS

Johns Hopkins and its licensees did not, for a substantial time, take any action to develop practical therapeutic applications of the Civin patents, nor is there any way they could now do so within a reasonable time. In the present context, "a reasonable time" necessarily means in time to provide patients with the benefits of products that provide the same benefits as CellPro's CEPRATE System, which is now FDA licensed and available in the United States. Given that it is likely to be at least two to three years before the FDA even determines whether the Baxter product is approvable, it is apparent that Johns Hopkins and its licensees have not acted within the required time frame.

Moreover, the lead that CellPro holds over other potential licenses is not an accident. Rather, it is the direct result of the fact that during the period that employees of the Hutchinson Center and CellPro discovered and developed the 12.8 antibody and the avidin-biotin column and began the tests -- first on baboons and then on humans -- that eventually led to FDA approval of the CEPRATE System, Johns Hopkins and its licensees essentially sat on the sidelines.[23/] Only after CellPro had demonstrated that stem cell transplants worked on human

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[23/] See the statements of Baxter's counsel in response to a question by the judge in the recent patent trial as to whether Baxter or Becton Dickinson was commercializing My-10 or other CD34 antibodies in 1990: "They hadn't even started to try, your Honor." "I don't think there's any evidence . . . Becton Dickinson attempted to develop a therapeutic product." "[In 1989, Baxter] said internally, This is a potentially valuable product. If we don't take this sublicense, somebody else will and do something valuable with it." "But my understanding is that the development efforts at Baxter didn't get under way until the latter part of '91 or the early part of '92." Transcript at 110-11, Baxter Healthcare Corporation, et al. v. CellPro, Inc., March 3, 1997 (Exhibit Volume I, Tab 12A). See also Testimony of John Osth, President of Baxter's

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patients did Baxter first develop a prototype product and begin the work needed to gain FDA approval. That delay and the unreasonable and adverse impact on the public that would result from the elimination or curtailment of the CEPRATE System while Baxter pursues its PMA application provides a second, independent statutory basis for the Department to grant the CellPro Petition and thus avoid an unconscionable disruption of the availability of a treatment to those in need of stem cell transplants as they battle breast cancer, lymphoma, multiple myeloma, leukemia, and other debilitating and often fatal diseases.

From information available to CellPro, it appears that it will be a lengthy period before Baxter is able to bring a comparable device to the market, if at all. According to testimony in the recent patent trial, Baxter filed a PMA application for its "Isolex 300" system on February 24, 1997, one week before that trial began.[26] Based upon the FDA's normal review procedures and timing, Baxter could not expect approval of its product for at least two years. According to statistics provided in the annual report of FDA's Office of Device Evaluation, the average elapsed time from submission to approval of a PMA at the Center for Devices and Radiological Health ("CDRH") was 786 days in Fiscal Year 1996.[27] The average elapsed time

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[25] (...continued)
Immunotherapy Division, Transcript at 299, id., March 5, 1997 (Exhibit Volume I, Tab 12B) ("And to be straight, the projects, such as -- as the utilization of the Curt Civin technology were kind of falling down on the priority scale. I think we all know that in big companies, that there are lots of priorities.")

[26] Testimony of John Osth, President of Baxter's Immunotherapy Division, Transcript at 311, Baxter Healthcare Corporation, et al. v. CellPro, Inc., March 5, 1997 (Exhibit Volume I, Tab 12B) ("It was done a week ago last -- a week ago Monday. We filed with the FDA for approval for our Isolex technology, our Isolex 300 technology").

[27] 1996 F.D.A. Office of Device Evaluation Annual Report at 17 (Exhibit Volume I, (continued...)

is up slightly from 773 days in Fiscal Year 1995, and an improvement on the Fiscal Year 1994 performance of 823 days. Thus, if the Baxter submission is indeed "average," approval could be expected in approximately 26 months. Given that Baxter filed in late February of 1997, this would mean the process would be completed in late April of 1999.

Even these predictions seem optimistic in the case of the Baxter PMA application, however. Baxter's filing, like CellPro's, will be evaluated not by the CDRH but rather by the Center for Biologics Evaluation and Review ("CBER"). In CellPro's experience, a review at CBER is even more extensive and likely to take even longer as evidenced by the fact that it took 3 years for the CellPro approval even with a prospectively designed, randomized clinical trial developed and implemented in close communication with the FDA. Also, from publicly available information, CellPro believes that the PMA is less than average in quality. There are likely many deficiencies in the submission, and there are significant questions about the product. This will almost certainly cause the FDA to demand additional studies. Preparing and conducting such studies will take months, if not years. Compiling and analyzing the data will take more time. If questions raised by the FDA are not sufficiently answered, the Baxter product may never reach the market.

To comprehend the issues involved in the Baxter application, it is important to understand the basic principles of operation of the Baxter system. In Europe, Baxter has sold two "Isolex 300" systems. The "Isolex 300SA" was the first stem cell product sold using the

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27/ (...continued)
Tab 13).

Baxter magnetic bead separation system. When attached to appropriate antibodies -- in the case of the Isolex system a sheep anti-mouse antibody, which in turn recognizes Civin's My-10 or another mouse anti-CD34 antibody -- the magnetic beads (which are much smaller than cells) are effective at selecting desired sub-populations of cells. When the bead system is used for "negative" cell selection, the beads, antibodies, and selected cells are simply removed. In "positive" selection, however, where the selected cells are intended to be given back to the patient (e.g. transplantation of bone marrow stem cells), the magnetic beads must be removed from desired cells prior to re-infusion. This is a complicated process.

In the Isolex 300SA system, the Baxter technology utilized a powerful enzyme known as chymopapain (used in meat tenderizer) to remove the beads from separated stem cells.[28/] Although the enzyme is effective in removing most of the beads, it also destroys proteins on the outside of the cells. This change in the surface of the cell could have a negative effect on how the cells function, additional immunophenotypic analyses or further immunoselection. Further, and more important, there is a real concern regarding adverse side effects from the enzyme. Indeed, one of the few published studies using chymopapain to release stem cells reports that one patient, a young adult, developed acute paraplegia on the first day after transplant.[29/] In addition, damage to cell surface antigens by chymopapain may interfere with the homing, growth, and survival of the CD 34 cells after the transplant patient received

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28/ See Baxter literature describing the Isolex 300SA (Exhibit Volume I, Tab 14).

29/ See Civin et al., Highly Purified CD34 - Positive Cells Reconstitute Hematopoiesis, Journal of Clinical Oncology, Vol. 14, No. 8, August 1996 (Exhibit Volume I, Tab 15).

them. Indeed, alteration of the cell surface structures can make the reinjected cell appear as foreign and may provoke an immune response against it.

Baxter recently developed a new system, which makes major engineering changes to the Isolex 300 in the hope of addressing these problems. The new product, known as the "Isolex 300i," does not use chymopapain but, rather, a peptide release technology designed to separate the beads from the cells without damaging the important extra cellular proteins. In introducing this new technology, Baxter emphasized that the Isolex 300i was a significant improvement over the Isolex 300SA, particularly in that it preserved cell surface antigens, "unlike enzymatic release mechanisms."[30/]

It is impossible for CellPro to know whether Baxter has sought FDA approval for the Isolex 300SA system, which is the first generation device, or for the more advanced Isolex 300i. If it is the Isolex 300SA system, employing chymopapain, CellPro believes that the FDA would require extensive studies to prove that the damage to proteins on the outside of the cells caused by the chymopapain does not impact upon the safety and effectiveness of the device. If the PMA being sought is for the Isolex 300i, which it would seem it should be given Baxter's apparent recognition that the Isolex 300SA is obsolete, there are serious concerns about the adverse impact of magnetic beads upon patients if there is not an absolute, 100 percent separation prior to infusion of the cells. There have been reports of a case where a patient treated with Baxter technology in Bath, England died of liver failure. CellPro understands that an autopsy was performed and beads were found in the liver of the patient. Although Baxter's

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30/ See Baxter literature describing Isolex 300i (Exhibit Volume I, Tab 16).

recent promotional literature seems to claim that no magnetic beads are present in solutions of stem cells separated with the Isolex 300i, it earlier had claimed only a reduction in the number of beads as compared to those in solutions obtained by using the Isolex 300SA.[31] Additionally, the FDA is likely to have questions about the combined use of mouse and sheep antibodies and about potential problems stemming from the complexity of the Isolex 300i, which has 22 valves, 4 pumps, 6 scales, and 2 pressure spinners. CellPro understands that various sites have reported numerous problems with the instrument and that when problems occur, it is difficult to save the bone marrow or peripheral blood with the result that there are no or insufficient cells to reconstitute the patient's blood and immune systems following intensive chemotherapy.

Based upon a search of all available literature, CellPro believes that the clinical information submitted by Baxter to support its PMA is inappropriate and insufficient. Specifically, it appears that there have been no randomized, controlled clinical trials. In a press release, Baxter indicated more than 800 patients have been treated in clinical trials at various centers in Europe and the United States using the Isolex 300 system. From published literature, it appears that this number may include patients treated on the Isolex 50 (the small scale laboratory prototype), the Isolex 300SA, and the Isolex 300i – three very different systems. These patients were not treated under a single protocol, and data were in most instances collected retrospectively.[32]

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[31] Id.

[32] See Boon Yap, Market Intelligence on Baxter Isolex 300 SA and Isolex 300 (November 26, 1996) (Exhibit Volume I, Tab 17). There are reports of one phase III randomized study conducted at sites in Europe and the United States. These reports indicate that the

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Since the report of the Temple Committee in March 1993, the FDA has insisted that clinical trials submitted in support of PMA applications be prospective, randomized, and controlled wherever possible. FDA will not accept "isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinion as valid scientific evidence to show safety and effectiveness."[33] This was made clear to CellPro as it submitted the PMA for its CEPRATE System product, and it will be made clear to Baxter.

Further, the FDA has required CellPro, and will require Baxter, to demonstrate that its product has beneficial, therapeutic effects. It will not be sufficient to show that the Isolex 300SA or Isolex 300i selects CD34 cells with engraftment equivalent to patients who receive unselected marrow. In the case of CellPro's Phase III clinical trials for approval of the CEPRATE System, the FDA has required a demonstration of reduced toxicity for its bone marrow submission (approved in December 1996) and a reduction in tumor cells for its supplemental peripheral blood submission (filing anticipated later this year). CellPro demonstrated the reduction in toxicity, and this was used as the basis of the initial FDA approval of the CEPRATE System. As noted above, CellPro has recently concluded its Phase III study

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[32] (...continued)
instrument used was the Isolex 300SA and that the accrual rate of the trial was slow. See C. Chabannon, et al., High-Dose Chemotherapy Followed by Reinfusion of Selected CD34+ Peripheral Blood Cells in Patients with Poor Risk Breast Cancer, (Exhibit Volume I, Tab 18); Shelly Heimfeld, Additional Information on Baxter Randomized Trial Described in ASH 1995 Abstract, (March 20, 1997) (two memoranda) (Exhibit Volume I, Tab 19). A report presented at the American Society of Clinical Oncology in 1996 noted "the use of technology may be limited by poor mobilization in a proportion of the candidates." Id.

[33] 21 CFR 860.7 (c)(2).

designed to demonstrate that its system dramatically reduces the number of tumor cells reinfused in cancer patients.

It is highly unlikely that Baxter included useable data on either reduced toxicity or reduction in tumor burden in its PMA submission. As noted above, it appears that their submission is based on data from patients treated in numerous centers in Europe and the United States. Information on toxicities associated with transplants is not routinely collected. While some information may have been collected on the reduction of tumor burden in the autografts of some patients, the methods used to determine tumor burden probably have varied from site to site, and would probably not be considered validated methods by the FDA.

In short, CellPro believes that it will be impossible for Baxter to submit sufficient data from the studies it has done. Therefore, Baxter will have to initiate new, prospective, randomized, controlled clinical trials. Enrolling patients for such trials would typically take about a year. If the FDA process is consistent with the requirements imposed upon CellPro, there will be a one year follow-up on the patients, and then data will be compiled, analyzed, and submitted. If all goes well, the process will likely take at least three years.

It should be recalled that Dr. Civin discovered his My-10 antibody in 1982. Since then, Johns Hopkins and its licensees have not been successful in taking the steps necessary to convert the discovery to a marketable product that would benefit the American people. Specifically, the time line for activities looks like this:

February 1984:	Civin files a patent application claiming his My-10 Antibody is therapeutically useful to transplant myeloblated patients.
August 1984:	Johns Hopkins, as Civin's assignee, licenses Becton-Dickinson under the filed application.
August 1990:	Becton-Dickinson sublicenses Baxter for therapeutic applications.
December 1992:	Baxter sublicenses Applied Immune Sciences.
November 1993:	Baxter sublicenses Systemix.
February 1997:	Thirteen years after the patent filing, Baxter files FDA application for PMA.
1999-2001:	Possible FDA approval of Baxter product.

Rather than expending effort to develop an effective product and take it to market, it appears that Becton-Dickinson focused all its efforts on diagnostic applications. When it finally sublicensed Baxter, that firm took no real action to begin development until CellPro rejected its attempt to condition a license for the Johns Hopkins patents on exclusive distribution rights to CellPro's products in Europe and Japan.[34]

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[34] Both of Baxter's sublicensees have since been acquired by large European pharmaceutical companies, and neither has an FDA approved product using this technology. AIS, now part of Rhine Poulenc Rhor Corp., appears to have abandoned the technology altogether. Systemix, recently acquired by Sandoz, is apparently years away from an approved product.

Contrast that performance with the aggressive and effective steps taken to exploit the discovery of the 12.8 antibody at the Hutchinson Center which occurred shortly after Dr. Civin filed his patent application. Dr. Berenson and others at the Hutchinson Center continued their studies and learned that the 12.8 antibody binds with baboon stem cells. Subsequent studies with baboons laid the groundwork for all subsequent studies with humans, led to the founding of CellPro in 1989, and resulted in the development of the CEPRATE System (after expenditure of 75 million dollars on research and clinical tests) which has been used to treat over thousands of patients worldwide since 1992. The CEPRATE System has been used for more than four times as many patients in Europe, notwithstanding that Baxter is a much larger company with a much larger sales force and that Baxter has been severely discounting the Isolex 300SA in an effort to gain market share. More importantly, CellPro (an example of the small, dynamic, kind of company which the Bayh-Dole Act's preference for small business licenses was aimed to inspire) has taken and continues to take the steps necessary fully to develop the potential of Dr. Berenson's discoveries and to make the resulting benefits available to patients in the United States. Developing and taking a breakthrough product through the PMA process is a very difficult task, particularly for a combination product. CellPro performed this task effectively and efficiently in less than seven years. Johns Hopkins and its licensees have failed to do so in almost twice that period.

In fact, some observers believe the Baxter submission to the FDA was not a serious filing but rather a last-minute strategic move to try to improve the appearance of its competitive position to improve its posture in the patent litigation and in proceedings regarding

march-in rights under the Bayh-Dole Act.[35] Indeed, Baxter is attempting to sell the division which developed the Isolex 300SA and Isolex 300i systems.[36] This raises further doubts as to whether Baxter will commit the extensive resources that will be needed to take the product through the approval process.

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In sum, while Baxter's submission to the FDA is not available to CellPro, CellPro believes, based on all of the information it has, that approval of the Baxter technology is, at minimum, years away. The Isolex 300SA has significant technical deficiencies and has not been successful in the European marketplace, and there are technical and other questions regarding the Isolex 300i. The bulk of the clinical data submitted appears to be based upon experience in non-randomized trials with the first product. Even if the data submitted were considered sufficient by FDA, it could not be applied to the Isolex 300i because that device relies on significantly different operating principles. To win approval for its products, CellPro believes that Baxter would have to begin its clinical studies anew.

Under these circumstances, there are simply no "effective" steps Baxter can take in a reasonable time to make products available to patients in this country if it forces CellPro's CEPRATE System from the market or limits its availability to physicians and their patients.

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[35] See Rich van den Broek, Will the Pain Ever End?, H&Q Spot Report at p.2 (March 13, 1997) (Exhibit Volume I, Tab 20).

[36] See Facsimile from Kevin Davies, Lehman Brothers, to Richard Murdoch, CellPro, attaching executive summary and confidentiality agreement related to the sale of the Immunotherapy Division of Baxter (February 25, 1997) (Exhibit Volume I, Tab 21).

Under the terms of Subsection (a) of the Bayh-Dole Act's provisions for march-in rights, there are very clear grounds for the Department of Health and Human Services to exercise such rights.

V. CONCLUSION

The Bayh-Dole Act provides that the Department of Health and Human Services may exercise its march-in rights and require that a license be issued if it determines that such action is necessary to alleviate public health needs or because the assignee of a patent has not taken effective steps to achieve practical application of the subject invention. In this instance both of these requirements have clearly been met. Unless enjoined, the CEPRATE System will be used to treat thousands of patients in this country who will have no other equally effective treatment option. In addition, in the thirteen years that first Becton-Dickinson and then Baxter have been licensed, they have not brought a product to the market. Because there can be no dispute regarding either the public health needs satisfied by the CEPRATE System or Baxter's failure to offer an FDA approved product, CellPro requests that the Department of Health and Human Services immediately exercise its march-in rights to require Johns Hopkins to issue CellPro a license to the Civin patents on reasonable terms or to issue such a license itself.