IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEXELL THERAPEUTICS, INC., BECTON DICKINSON AND COMPANY, and THE JOHNS HOPKINS UNIVERSITY,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 00-141-RRM
AMCELL CORPORATION, MILTENYI BIOTECH, INC., and MILTENYI BIOTECH GMBH,	)	
Defendants.	)	

OPINION

Richard H. Morse, Esquire and Josy W. Ingersoll, Esquire, Young Conaway Stargatt & Taylor LLP, Wilmington, Delaware; Karen J. Kramer, Esquire, Law Offices of Karen J. Kramer, Somers, New York; Willem G. Schuurman, Vinson & Elkins, Austin, Texas; counsel for plaintiffs.

Philip A. Rovner, Esquire, Potter Anderson & Corroon LLP, Wilmington, Delaware; Donald R. Ware, Esquire, Clare Laporte, Esquire, and Robert L. Bocchino, Jr., Esquire, Foley, Hoag & Eliot LLP, Boston, Massachusetts; James W. Inskeep, Esquire, Oppenheimer Wolff & Donnelly LLP, Newport Beach, California; counsel for defendants.

Dated: April 23, 2001

McKELVIE, District Judge:

This is a patent case. The Johns Hopkins University is a Maryland non-profit corporation with its principal place of business in Baltimore, Maryland. Johns Hopkins owns U.S. Patent Nos. 4,714,680 (the ’680 patent) and 4,965,204 (the ’204 patent). These patents are known collectively as the Civin patents, named after their inventor, Dr. Curt Civin, a physician and professor at The Johns Hopkins University School of Medicine and The Johns Hopkins University Hospital in Baltimore, Maryland. The patents disclose a method to prepare purified suspensions of human stem cells through the use of specific antibodies for therapeutic use in transplantation and other procedures.

Johns Hopkins granted an exclusive license to use the Civin patents to Becton, Dickinson and Company, a New Jersey Corporation with its principal place of business in Franklin Lakes, New Jersey. Becton Dickinson thereafter granted an exclusive license to Baxter Healthcare Corporation, which in turn conveyed its rights under the Civin patents to Nexell Therapeutics, Inc., a Delaware corporation with its principal place of business in Irvine, California.

Nexell produces the Isolex system, a magnetic cell separation device. When used in conjunction with the antibodies identified in the Civin patents, this product can separate stem cells from peripheral blood cells and bone marrow for transplantation and other therapeutic uses. This device has been approved by the Food and Drug Administration (FDA) for commercial sale in the United States.

Defendant AmCell Corporation is a Delaware corporation with its principal place of business in Sunnyvale, California. Defendant Miltenyi Biotec, Inc. is a California corporation with its principal place of business in Auburn, California. Defendant Miltenyi Biotec GmbH is a German corporation with its principal place of business in Germany.

Miltenyi Biotec GmbH developed MACS, a magnetic cells separating technology. Based on MACS, AmCell produces CliniMACS, a device which permits large-scale magnetic cell separation. Miltenyi Biotec GmbH holds a license from Becton Dickinson to use the antibodies in the Civin patents for in vitro research. The license agreement excludes the use of the antibodies for in vivo therapeutic research.

On March 1, 2000, Nexell, Becton Dickenson, and Johns Hopkins filed a complaint against AmCell, Miltenyi Biotec, Inc., and Miltenyi Biotec GmbH alleging that by selling or offering to sell the CliniMACS device for use with certain antibodies, defendants infringed or actively induced others to infringe the Civin patents, breached the license agreement, and engaged in unfair competition.

On April 24, 2000, Miltenyi Biotec, Inc. and Miltenyi Biotec GmbH moved to dismiss the complaint pursuant to Fed. R. Civ. P. 12(b)(2) on the ground that this court lacks personal jurisdiction over them and under Fed. R. Civ. P. 12(b)(4) and (5) for insufficient process and insufficient service of process. The same day, AmCell answered the complaint and counterclaimed that Nexell, Becton Dickinson, and Johns Hopkins engaged in unfair competition and moved for a declaratory judgment that AmCell did not

infringe the Civin patents or breach the license agreement. Because of ongoing jurisdictional discovery, the plaintiffs have not responded to the motions to dismiss. On May 16, 2000, plaintiffs replied to AmCell's counterclaims.

On November 8, 2000, AmCell moved for a summary judgment of non-infringement. On December 18, 2000, Nexell, Becton Dickinson, and Johns Hopkins moved for a partial summary judgment of infringement against AmCell, Miltenyi Biotec, Inc., and Miltenyi Biotec GmbH. Sections 271(a), (b), and (c) of the patent statute set out grounds for liability for infringement, active inducement to infringe, and contributory infringement. Section 271(e)(1) lays out an exemption from infringement for activities related to obtaining regulatory approval. Plaintiffs claim that defendants infringe under §§ 271(a), (b), and (c) and that defendants' actions are not protected by the exemption in § 271(e)(1). AmCell claims that it does not infringe the Civin patents under 35 U.S.C. § 271(e)(1) because it is pursuing approval from the FDA for use of the CliniMACS device in conjunction with antibodies covered by the Civin patents.

The court heard oral arguments on these motions on January 31, 2001. This is the court's decision on those motions.

I. FACTUAL BACKGROUND

The court draws the following facts from the pleadings in this case; the affidavits, transcripts of depositions, and answers to interrogatories offered by the parties in support of and in opposition to the pending motions; and the court's previous opinion construing the claims of the Civin patents, see Johns Hopkins Univ. v. CellPro, 931 F. Supp. 303 (D. Del. 1996) aff'd in relevant part, 152 F.3d 1342 (Fed. Cir. 1998).

A. The Technology

The Civin patents pertain to pure suspensions of immature blood cells, known as stem cells, and the monoclonal antibodies used to produce the suspensions. Stem cells are a vital part of bone marrow and can develop into many different forms of mature blood cells. Blood consists of plasma, a liquid that makes the blood fluid and that contains proteins for clotting, and certain blood cells–red cells, platelets, and white cells. Red cells carry oxygen in the blood. Plateletes cause blood to clot. White cells help fight infections and are part of the immune system. White blood cells are further divided into two large families: lymphocytes and granulocytes. There are different types of lymphocytes such as T lymphocytes, also known as T cells, and B lymphocytes, also known as B cells. T cells govern certain immune responses and are the cells that are destroyed by the AIDS virus. B cells make antibodies, which are important for fighting certain types of infections.

Blood cells have a short life span, and thus the body must produce millions of blood cells each day. Blood cells are manufactured in the cavity of some bones in a

tissue known as bone marrow. Some cells, known as pluripotent or multipotent stem cells, exist in bone marrow and can create a number of different types of cells. A stem cell produces other cells by dividing over and over until thousands of cells have been manufactured.

Stem cells are called immature because they have not determined what type of cell they will become. A stem cell may become a lymphoid stem cell that can later become a B or T cell. Alternatively, a stem cell can become a myeloid stem cell that can later become a red cell, a platelet, or a granulocyte. Stem cells are very rare and difficult to locate. Over time, stem cells become progressively more "differentiated," which is the word used to describe blood cell maturation. Lymphoid and myeloid cells differentiate into progenitor cells, which are uncommon but not as rare as stem cells. Progenitor cells still retain some ability to reproduce different kinds of cells. For simplicity, the court will refer to both progenitor cells and stem cells as stem cells.

When successful, bone marrow transplantation is an effective therapy for an increasing number of diseases. However, several factors limit the success and utility of bone marrow transplantations. First, using bone marrow from another individual can result in Graft Versus Host Disease (GVHD), in which the T cells produced by the transplanted marrow attack the patient's body. This disease can be disfiguring and lethal. One method of avoiding GVHD is to use the marrow of a patient's sibling whose tissue matches the patient's. Even then, approximately half of the transplant recipients develop GVHD. To avoid GVHD doctors could use bone marrow from the patient. However,

this also poses substantial risks as it leaves open the possibility of putting infected or cancerous cells that remain in the removed marrow back into the patient. Given these risks, doctors therefore commonly use bone marrow transplantation only in patients with an otherwise fatal disease, such as cancer, aplastic anemia, and congenital immunodeficiency states.

Lastly, bone marrow transplantation is limited as a therapeutic option because current harvesting techniques subject donors of bone marrow to undesirable procedures and risks. Bone marrow transplantation can be painful and expensive and can expose the donor to infection and risks associated with blood transfusion.

In order to extend the use of bone marrow transplants, Civin sought a method to reduce or eliminate GVHD associated with bone marrow transplants. Civin wanted to isolate stem cells, the helpful cells in the transplantation process, from T cells or other peripheral blood cells that would be unnecessary or unwanted in bone marrow transplants.

Civin knew that in the early 1980s, scientists developed a method to identify and isolate blood cells in order to learn about diseases related to these cells. Scientists observed that antibodies may provide a method to identify specific cellular structures. As noted above, antibodies fight infections, such as bacteria. If a bacteria is present in the body, B cells will produce antibodies that bind to one side of the bacteria known as an antigen. Since antigens are often larger than antibodies, antibodies sometimes connect with only a portion of the antigen, known as an epitome. Blood cells, like bacteria, have

antigens as well. Therefore, antibodies can also bind to blood cells that have the appropriate antibody.

There are many different types of antibodies, such as IgG and IgM monoclonal antibodies. Monoclonal antibodies have different characteristics, but all monoclonal antibodies have an antigen-specific binding site, each antibody will only bind to one type of antigen. That is, although many antigens can bind to multiple antibodies, in part because of the existence of multiple epitomes on a single antigen, each antibody will bind to only one antigen.

Civin identified an antigen that appears on the surface of immature stem cells, but not on the surface of mature cells. This antigen is stage specific, such that it appears only in the stem cells, but not mature cells. But, the antigen is not lineage dependant, in that it was found on many different types of immature cells. Civin then created an antibody to bind to that antigen.

Civin knew that there were several techniques available to separate the stem cells that bound with his new antibody. In one such process called Fluorescence-activated coating separation (FACS), scientists coat the antibodies with a colored dye, and use a laser to identify and separate the cells based on their color. In another technique called panning, scientists place the antibodies and the cells in a petri dish, a laboratory dish generally made of plastic. The antibodies bind to the cells on the appropriate antigen and adhere to the plastic. The remaining cells float free in the petri dish and can be washed away.

The Civin patents identify the discovered antigen as the My-10 antigen and the monoclonal antibody that binds to that site as anti-My-10 antibody. Other scientists subsequently produced antibodies that bound to the My-10 antigen. At the International Leukocyte Workshops, a series of information sharing scientific seminars, scientists set up clusters of antibodies that labeled the same antigen or set of cells. The My-10 antigen was given the designation CD-34 because it was the 34th cluster designation of an antigen. Thus, the anti-My-10 antibody was and is called a CD34 antibody.

The '204 patent claims the CD34 monoclonal antibodies that specifically bind to the CD34 antigen. The '680 patent claims a highly purified suspension of human stem cells that is substantially free of mature lymphoid and myeloid cells.

B. The Regulatory Framework

Congress classifies medical devices in three categories based on the risk of their use. See The Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-395 (1994). Devices that do not "present an unreasonable risk of illness or injury" and are not "purported or represented to be for a use in supporting or sustaining human life" are designated Class I and are subject to minimal regulation by "general controls." 21 U.S.C. § 360c(a)(1)(A); see also Medtronic, Inc. v. Lohr, 518 U.S. 470, 476-77 (1996). "Devices that are potentially more harmful are designated Class II; although they may be marketed without advance approval, manufacturers of such devices must comply with federal performance regulations known as 'special controls.'" Medtronic, Inc., 518 U.S. at 477 (quoting 21 U.S.C. § 360c(a)(1)(B)). Lastly, "devices that either 'present a

potential unreasonable risk of illness or injury,' or which are 'purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health,' are designated Class III." Id. (quoting 21 U.S.C. § 360c(a)(1)(C)).

The FDA classifies both Isolex and CliniMACS as Class III, or significant risk, medical devices. As a general rule, Class III devices may not be shipped in interstate commerce for use in human subjects without meeting performance standards or pre-market approval of the device. However, if the FDA grants an Investigational Device Exemption (IDE), the manufacturer may ship the device for investigational use in accordance with an FDA-approved protocol. See 21 C.F.R. § 812.1.

Manufacturers and clinical investigators can seek and obtain IDEs (respectively called company-sponsored IDEs and investigator-sponsored IDEs). According to Dr. Bonnie Mills, a Senior Director of Clinical and Regulatory Affairs at Nexell, companies and investigators have different incentives to seek an IDE. Manufacturers conduct clinical trials pursuant to company-sponsored IDEs in order to generate data that will allow the company to obtain FDA approval for the device. Researchers seek IDEs in order to investigate potential uses of a device that are of particular clinical interest to them.

According to declarations submitted by the plaintiffs from Mills and Dr. Joy Cavagnaro, the president of Access BIO, a regulatory consulting firm, manufacturers seeking approval from the FDA for a Class III device generally propose an investigational

plan for clinical testing of the device to the FDA. The investigational plan must include a written protocol demonstrating that the investigation is scientifically sound, a risk analysis justifying the investigation, a detailed description of the device, and written procedures for monitoring the investigation. See also 21 C.F.R. § 812.25. After the FDA reviews the plan and grants an IDE, the manufacturer may begin the clinical trials. The manufacturer must oversee and monitor the trials to ensure that the studies generate consistent, reliable data that can be used to support an application for pre-market approval. Cavagnaro contends that the FDA has admonished companies to adopt a focused development plan designed to generate only the clinical data needed to support approval of the investigational device as quickly as possible and without needlessly exposing patients to an unapproved device.

Investigators can also obtain IDEs from the FDA. Mills and Cavagnaro state that in contrast to the company-sponsored IDEs, clinicians who seek investigator-sponsored IDEs do not face the same regulatory barriers as manufacturers that seek company-sponsored IDEs. That is, although the FDA requires clinical investigators to submit a plan of investigation, because the plan involves a single site with a limited number of patients, the FDA's review of the plan is less rigorous. Further, an investigator need not tailor his or her research to obtaining approval for the device, rather the investigator can focus on his or her own areas of interest. Before an investigator can get specific approval for an investigator-sponsored trial from the FDA, the investigator must first develop a protocol and get preliminary approval from the manufacturer. See 21 C.F.R. § 812.3.

This type of trial is in contrast to a company-sponsored trial in which the company develops the protocol and requires the investigator to follow the company's plan.

C. Nexell's Commercialization of the Civin Patents

Johns Hopkins owns the Civin patents and granted an exclusive license to Becton Dickinson to use these patents. Becton Dickinson, in turn, granted an exclusive license in the fields of therapy and therapeutic research to Baxter Healthcare.

In 1990, Baxter began developing a commercial cell separation device based on the Civin patents. According to plaintiffs, Baxter spent tens of millions of dollars to develop a safe and effective cell separation device to purify human stem cells from blood and bone marrow for use in cancer therapy and other therapeutic procedures.

In February 1997, after controlled and monitored clinical trials, Baxter filed an application for pre-market approval for its cell separation device, the Isolex system, with the FDA. The Isolex system uses magnetic particles conjugated to CD34 monoclonal antibodies to isolate stem cells from peripheral blood or bone marrow. Shortly thereafter, Baxter spun off its Immunotherapy Division as Nexell Therapeutics, Inc. Baxter conveyed its rights to the Civin patents and to Isolex to Nexell.

On July 2, 1999, the FDA approved the Isolex system for commercial sale.

D. AmCell and MACS Technology

In 1993, AmCell was founded to commercialize clinical applications of MACS, a magnetic cell separation technology developed by Miltenyi Biotec GmbH. MACS technology uses submicroscopic superparamagnetic particles bound to antibodies to

isolate purified cell subpopulations using high gradient magnetic cell separation columns. According to Richard Reeves, vice president and general manager of AmCell, devices based on MACS technology can be used with a variety of reagents for the purpose of identifying and isolating a variety of cells. Among these reagents is the CD34 antibody.

Originally, commercialization of MACS systems was to be a collaborative effort among Miltenyi Biotec GmbH, Amgen, Inc., and AmCell. Miltenyi Biotec GmbH was responsible for developing the underlying technology, Amgen was responsible for conducting clinical trials and carrying out the regulatory approval process, AmCell was responsible for coordinating the project and further developing the product.

The CliniMACS system, based on MACS technology, is the outgrowth of this collaboration. CliniMACS permits automated large scale magnetic cell selection in a closed and sterile system. In 1996, Amgen began the process of applying to the FDA for approval of a company-sponsored IDE that would allow it to conduct trials of the CliniMACS system.

Beginning in February 1996, Amgen conducted a 60-patient trial of the device to prepare for the FDA approval process and to obtain CE Mark approval in Europe. Amgen conducted this study at three sites in the European Union to assess the safety of using positively selected cells from the CliniMACS system in breast cancer patients undergoing high dose chemotherapy requiring progenitor cell support. Amgen collected the data in accordance with relevant United States and European Union regulations.

On September 18, 1996, Amgen sent the FDA a pre-IDE background package that included a proposed investigational plan. The package reported on the progress of the European study and requested guidance from the FDA on the design of the plan, including questions regarding whether the proposed endpoints, number of patients, and number of sites would be satisfactory to support pre-market approval. In addition, the pre-IDE package included a proposal for two additional clinical investigations that would support pre-market approval, one for breast cancer and one for lymphoma.

In September 1997, Amgen, Miltenyi Biotec GmbH, and AmCell terminated their collaboration. The rights and responsibilities concerning CliniMACS reverted to AmCell. AmCell manufactures CliniMACS in Germany at a wholly owned subsidiary. AmCell also developed a product called Research CliniMACS, which is available for use by scientists for in vitro research. According to plaintiffs, AmCell obtained regulatory approval to market its CliniMACS in Europe in 1997, and currently sells it throughout Europe.

In 1998, Becton Dickinson granted Miltenyi Biotec GmbH and its affiliates a license to use the CD34 antibodies disclosed in the Civin patents for in vitro research use. Reeves stated in his declaration that Miltenyi Biotec, Inc. and AmCell are affiliates of Miltenyi Biotec GmbH under this license. Miltenyi Biotec, Inc. markets reagent kits in the United States containing CD34 MicroBeads, which are CD34 antibodies bound to Miltenyi Biotec, Inc.'s superparamagnetic particles.

According to plaintiffs, on October 2, 1998, Reeves sent the FDA information on behalf of AmCell about the "manufacturing methods, materials, processes, test methods, and results of two key components" of CliniMACS. In this letter, Reeves stated that the attached material contained trade secrets and asked that the FDA designate the information as the master file. A master file is a reference source on a manufacturer's device that the manufacturer submits to the FDA. See 21 C.F.R. § 814.3(d). Defendants contend that on November 24, 1998, AmCell filed a master file with the FDA for use of the CliniMACS system in conjunction with CD34 (the court will refer to use of the CliniMACS system exclusively with the CD34 antibody as CliniMACS/CD34). Reeves stated in his declaration that clinical investigators who wish to use the CliniMACS/CD34 system for investigator-sponsored trials must refer to the master file in communications with the FDA.

Reeves further stated in his declaration that in 1998, AmCell contacted several contract research organizations with the intent of hiring a third party to monitor and collect the clinical data in a manner acceptable to the FDA. The FDA requires clinical data meet the test of "valid scientific evidence." See 21 C.F.R. §§ 860.7(b)(4)(c)(2); 860.7(b)(4)(e)(2). According to Reeves, the use of a third party professional organization to collect, review, summarize, and analyze the data offers further assurance of meeting the FDA requirement.

In 1999, defendants began to recruit clinicians to participate in studies to evaluate the safety and effectiveness of the CliniMACS/CD34 systems. Miltenyi Biotec, Inc. sent

a letter to clinicians throughout the United States that solicited participation in the testing of CliniMACS/CD34. The letters stated that clinicians interested in using CliniMACS/CD34 would have to file an application with the FDA for an investigator-sponsored IDE (which AmCell would assist in preparing); obtain approval from the FDA; and keep, record, and distribute accurate data on the patients' reactions.

Plaintiffs claim that Miltenyi Biotec, Inc. maintains a database of approximately 1,000 names of clinicians that have expressed an interest in CliniMACS and that Miltenyi Biotec, Inc. sent solicitation letters as part of a pattern of recruitment to each of these clinicians. Plaintiffs contend that Miltenyi Biotec, Inc. also sent physicians packets that included efficacy claims about CliniMACS and information about how to order the device.

According to plaintiffs, defendants' recruiting efforts went beyond the solicitation packages. Plaintiffs contend Miltenyi Biotec, Inc. promoted CliniMACS at trade shows and in industry publications. For instance, plaintiffs claim that at the American Society of Hematology conference in December 1999, Miltenyi Biotec, Inc. maintained a booth featuring a display of the CliniMACS device with a sign titled, "CliniMACS–The better alternative." The bottom of the sign stated, "Master File submitted to FDA in USA; Now ready to accept IDE clinical protocols."

Plaintiffs also contend that defendants advertised CliniMACS for use in the medical journals. Plaintiffs point to Volume 1, Number 3 of Cytotherapy, which contains an advertisement that states CliniMACS is "best for clinical use" and has the "highest

purity and recovery of CD34+ cells for fast engraftment," "4-5 log T cell depletion," and the "most efficient tumor cell purging." The advertisement contained a disclaimer at the bottom that stated that CliniMACS is limited to use under an IDE in the United States.

Lastly, plaintiffs contend that the defendants used their websites as a means of solicitation. As early as March 1999, AmCell's website, <www.amcell.com>, made the following claims relating to CliniMACS:

> Regardless of the source of hematopoietic cells (mobilized or unmobilized peripheral blood, bone marrow, or umbilical cord blood), the CliniMACS leads the field in CD34 cell selection with excellent purities and yields in the selected cell population. . . . . The device is uncomplicated and easy to use, with a processing time of approximately two and one half hours.

According to plaintiffs, this language constitutes an efficacy claim about CliniMACS which violates FDA regulation. AmCell's website provided a small disclaimer that the device was not approved for sale in the United States. In July 2000, the FDA ordered AmCell to modify its web site by partitioning the site into two sections, one for clinicians in the United States and one for clinicians abroad. Further the FDA required AmCell to remove the above quoted language from the site directed toward clinicians in the United States. Miltenyi Biotec also maintains a website, <www.miltenyibiotec.com>, that contains general information about the MACS technology and CliniMACS in particular. Although the website does not partition information about MACS for clinicians inside the United States and those abroad, it does partition information about CliniMACS. Plaintiffs contend that these websites serve to market MACS and CliniMACS in the United States.

Beginning in May 1999, AmCell and Miltenyi Biotec, Inc. received over 80 protocols from clinicians interested in using CliniMACS/CD34 for clinical procedures. Because CliniMACS used in conjunction with the CD34 antibodies has the potential to remove T cells (which, as discussed above, can create barriers to transplantations) from heterogeneous blood samples, physicians proposed using CliniMACS/CD34 in a broad range of treatments including treatment of autoimmune disorders, leukemia, hemolytic anemia, late stage cancer, potentially mismatched organs, and gene therapy. After approving the protocols, AmCell would provide a cross reference letter to the FDA. This letter would allow the clinical investigator to cross reference AmCell's master file to support the investigator's application for an IDE.

Out of the 80 applications, AmCell selected 35 clinicians to apply to the FDA for permission to conduct investigator-sponsored clinical trials. Of the 35 clinicians that prepared protocols and submitted them to the FDA, the FDA approved 19 and failed to approve the remaining 17. It is not clear why the FDA did not approve 17 of the applications. At oral argument, AmCell's counsel suggested that the FDA may have rejected these applications for minor technicalities or because the FDA disagreed with some of the conditions in the clinician's protocol. Some of the institutions applied for and received more than one investigator-sponsored IDE. Therefore, AmCell has only installed 15 CliniMACS/CD34 systems for the 17 clinical trials. Plaintiffs contend that the CliniMACS/CD34 system has been provided to 29 other institutions. Defendants contend that these installations are for use of CliniMACS/CD34 under the Becton

Dickinson license agreement for in vitro research. Thus, according to defendants, these 29 installations are not subject to FDA approval, do not infringe the Civin patents, and are not relevant to this suit.

AmCell provides the CliniMACS device to FDA-approved clinical investigators for free. Pursuant to 21 C.F.R. § 812.7, AmCell provides the CD34 clinical reagent kits to the investigators on a cost recovery basis. That is, AmCell has not charged a price higher than that necessary to recover costs of manufacture, research, development, and handling of the product.

On June 10, 1999, representatives of AmCell met with the FDA to discuss a clinical trial AmCell wished to begin within six months. At that meeting, the FDA requested that AmCell submit an IDE. An FDA representative claimed that "the FDA could be of great help in the design of the trial." Linda Traylor, AmCell's Manager of Regulatory Affairs, stated at that meeting that AmCell would submit a company-sponsored IDE. Plaintiffs claim that AmCell did not file an IDE for over a year.

On October 13, 1999, AmCell hired Pacific Data Designs to manage data from the clinical trials. Reeves stated that Pacific Data Designs has conducted several projects for AmCell since that date, including auditing the European study from 1996 and collecting and analyzing the data from the clinical sites of investigator-sponsored trials in the United States.

On March 30, 2000, the FDA sent a letter to Traylor at AmCell regarding concerns about the investigator-sponsored IDEs in the master file. The letter stated in relevant part:

> We wish to notify you of significant concerns regarding numerous sponsor-investigator Investigational Device Exemptions (IDEs) referencing your Type II [master file]. We are concerned that such studies will not provide useful information in support of the clinical development of the device, and are subject to disapproval under 812.30(b)(4) due to deficiencies in study design. In addition, such IDE studies are in violation of 812.7(c), unduly prolonging the investigation of an investigational device.
>
> We note that you have failed to provide any plan for development of this device in support of a pre-market approval application (PMA). This topic (an investigational device development plan for the CliniMACS device) was the subject of pre-Phase 3, pre-IDE meeting between representatives of Amgen and [the FDA] held on October 29, 1996. We also note that you indicated, during the June 10, 1999, telephone conversation between you and Drs. Marjorie Shapiro and Elizabeth Shores of this Office, your intent to submit a plan for investigational development for this device within six months. Additionally, during the November 10, 1999 telephone conversation between you and Ms. Debra Beitzell of this Office, you indicated your intent to submit a pre-Phase 3, pre-IDE meeting request. No such meeting request or investigational plan has been received. While you have supplied your device to more than 20 academic investigators during this time, the studies are not appropriately designed to provide significant meaningful new information regarding the safety, performance standards, or effectiveness of the device.
>
> . . .
>
> Please be aware that effective the date of this letter, only studies that we consider to be appropriately designed to support a PMA will be approved. IDE studies that are not scientifically sound in the context of device development, and will thus result in prolonging the investigation of your device, will be disapproved under 21 C.F.R. 812.30(b). Therefore, we request that you refrain from supplying your device to investigators except as part of your investigational plan following agreement by the Agency.
>
> We also remind you that 21 C.F.R. 812.7 prohibits promotion and commercialization of an investigational device or representing that an

> investigational device is safe or effective for the purposes for which it is being investigated.

On May 23, 2000, AmCell submitted a "Pre-IDE Meeting Package" to the FDA. The package contained a general description of MACS technology, an environmental assessment, the marketing history of the device, and a risk analysis. In addition, the package contained a report of prior investigations, and a clinical development plan.

On June 20, 2000, representatives of AmCell met with representatives of the FDA. Among those in attendance at that meeting on behalf of AmCell were Stefan Miltenyi; Richard Reeves; Linda Traylor; Virginia Perry, a regulatory affairs consultant; John Kennedy, a biostatistician; and Karen Kramer, one of AmCell's attorneys in this matter. According to the meeting minutes drafted by Charles McKeever, a Regulatory Project Manager with the FDA/Center for Biologics Evaluation and Research, the FDA expressed concern with the design of the clinical trials and stated that AmCell must shift the approach and focus of the trials to "benefit to the patient, i.e., reduction in incidence of GVHD with equivalent survival." The FDA further stated that AmCell would have to reevaluate the role of investigator-sponsored trials in the clinical development plan. Specifically, the FDA stated, "AmCell needs to identify which sponsor-investigator trials they believe can contribute to their clinical development plan. These trials need to have credible data sets and AmCell needs to have complete, full access to the data. These data would be considered pilot data and, at best, could support safety." Further the FDA cautioned, "[t]here is a point at which further feasibility studies are no longer necessary

and ongoing studies need to be completed. These ongoing studies and their endpoints need to be identified in order to establish a uniform protocol for all sponsor-investigator sites."

On September 13, 2000, AmCell submitted a clinical development plan to the FDA. The plan included a clinical development time line, protocol synopses of proposed company-sponsored clinical trials, a product development plan, and a summary of investigator-sponsored trials. The plan called for AmCell to submit three new company-sponsored IDEs on October 31, 2000; November 17, 2000; and December 31, 2000. These IDEs would be for research in non-Hodgkin's lymphoma.

II. DISCUSSION

Plaintiffs contend that the defendants have infringed claims of the '204 patent under 35 U.S.C. § 271(a) by selling or offering to sell the CliniMACS device for use with the CD34 reagent within the United States. Further, plaintiffs claim that when clinicians use the CD34 reagent supplied by the defendants in conjunction with the CliniMACS devices to create purified cell suspensions, those clinicians directly infringe on claims of both the '204 and '680 patents. According to plaintiffs, by providing the CliniMACS marketing materials the defendants actively induce the clinicians to infringe under 35 U.S.C. § 271(b) and this activity also constitutes contributory infringement under 35 U.S.C. § 271(c).

AmCell contends that its activities are exempt from infringement under 35 U.S.C. §§ 271(a), (b), and (c) because pursuant to 35 U.S.C. § 271(e)(1) the sales of CD34 reagent are related to the development and submission of information to the FDA for regulatory approval of the CliniMACS device for use in conjunction with CD34 antibodies.

The relevant portions of the statute state:

> 271. Infringement of patent
> (a) Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.
> (b) Whoever actively induces infringement of a patent shall be liable as an infringer.
> (c) Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.
> . . .
> (e)(1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

A. Standard for Summary Judgment

Plaintiffs and AmCell have cross moved for summary judgment on the issue of infringement, however, the court, will consider them as motions for summary judgment on the applicability of the exemption found in § 271(e)(1). Summary judgment is proper if no genuine issue of material fact exists and the moving party is entitled to a judgment as a matter of law. See Fed. R. Civ. Pro. 56(c). "[T]he substantive law will determine which facts are material. Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude summary judgment." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). A dispute is genuine "if the evidence is such that a reasonable jury could not return a verdict for the nonmoving party." Id.; Apple Computer, Inc. v. Articulate Sys., Inc., 234 F.3d 14, 19-20 (Fed. Cir. 2000).

B. 35 U.S.C. § 271(e)(1)

1. Development of § 271(e)(1)

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585, which amended the FDCA and the patent laws, in response to two unintended distortions of the patent term produced by the requirement that certain products receive pre-market regulatory approval. See Eli Lilly and Co. v. Medtronic, Inc., 496 U.S. 661, 665 (1990).

First, as a practical matter the holders of a patent related to a device or drug subject to regulatory approval could not recover any monetary value for their product in the early term of the patent because the process of seeking regulatory approval kept the

product out of the market. See id. at 669. Section 201 of the 1984 Act provided an extension of the patent term for these products if the product was "'subject to a regulatory review period before its commercial marketing or use,' and 'the permission for the commercial marketing or use of the product after such regulatory review period [was] the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred." Id. at 671 (quoting 35 U.S.C. § 156(a)).

Second, Congress sought to reverse a decision by the Federal Circuit that affected the other end of the patent term. In Roche Products, Inc. v. Bolar Pharm. Co., 733 F.2d 858, cert. denied, 469 U.S. 856 (1984), the Federal Circuit determined that even activity aimed at seeking regulatory approval could constitute patent infringement. Thus, the patent holder gained an additional period to control the market at the end of its patent term while competitors sought regulatory approval for their products. See Eli Lilly and Co., 496 U.S. at 670. Section 271(e)(1), enacted as § 202 of the 1984 Act, addressed this concern. As a result of this amendment, a manufacturer who anticipates entering a market with a product covered by a patent held by a competitor may make, use, offer to sell, and sell that product so long as it is "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1); see also Telectronics Pacing Sys. Inc. v. Ventritex, Inc., 982 F.2d 1520, 1525 (Fed. Cir. 1992). Although not explicit in the statute, the Supreme Court has held that

this exemption applies to Class III medical devices, like those at issue here. See Eli Lilly and Co., 496 U.S. at 679.

2. Does the § 271(e)(1) exemption apply to AmCell's activities?

The FDA has not granted AmCell pre-market approval for the CliniMACS device for use in the United States. Nonetheless, AmCell has provided an opportunity for clinicians to use the CliniMACS device in conjunction with the CD34 antibody if clinicians are willing to apply for investigator-sponsored IDEs. In an effort to recruit clinical investigators, AmCell has advertised the availability and effectiveness of its device on its website, in medical and scientific journals, at academic conferences, and at trade shows. AmCell also sent CliniMACS/CD34 information packets to clinicians who expressed an interest in using and testing the device.

Nexell contends that AmCell infringes the claims of the Civin patents because these activities constitute an offer to sell under § 271(a). Further, Nexell contends that AmCell actively induces the clinicians to infringe and contributes to the infringement of the Civin patents by providing clinicians the CD34 antibodies with the CliniMACS device.

AmCell argues that it does not infringe the Civin patents because its activities are covered by the § 271(e)(1) exemption. That is, all of its activities are "reasonably related to the development and submission of information" to the FDA for approval of the CliniMACS device for use in conjunction with CD34 antibodies. Because the FDA has classified the CliniMACS system as a Class III medical device, AmCell must present data

to the FDA to show that CliniMACS/CD34 is safe and effective in order to gain approval for commercial use of the device. AmCell claims that § 271(e)(1) allows it to create and submit such data without infringing the Civin patents. Further, according to AmCell, each of the investigator-sponsored IDEs that Nexell has identified as a basis for claiming that AmCell infringes or induces others to infringe the Civin patents is aimed towards developing the necessary data. Therefore, AmCell claims it does not infringe the Civin patents.

Nexell counters that while AmCell may be seeking approval of CliniMACS/CD34, the real purpose of its activities is to market its device to physicians, and, in doing so, has exceeded the scope of the exemption in § 271(e)(1). As evidence of this, Nexell argues that defendants have engaged in heavy promotional and marketing activities that cannot be reasonably related to obtaining FDA approval. At the core of Nexell's argument is its concern that the defendants are undercutting its Isolex product and eviscerating the Civin patents by giving away the CliniMACS device for free and selling the CD34 reagent at cost. That is, Nexell contends that AmCell is promoting and soliciting investigator-sponsored IDEs of CliniMACS/CD34, not to gain FDA approval for the device, but to gain brand loyalty from clinicians. Further, because AmCell is giving away the CliniMACS machines and selling the reagent at cost, clinicians are more likely to chose that product over Isolex.

This issue comes before the court on cross motions for summary judgment. The parties agree that there are no genuine issues of material fact in dispute. While the parties

may disagree about the number of clinicians using the CliniMACS devices in conjunction with the CD34 reagent, the parties do not dispute that the FDA has approved approximately 17 investigator-sponsored IDEs at 13 institutions. Likewise, the parties may dispute the motive behind, but not the existence of, defendants' CliniMACS information packets and informational letters to physicians, defendants' advertisements in trade publications, and defendants' claims regarding CliniMACS on the defendants websites.

The Federal Circuit has construed the § 271(e)(1) exemption broadly. In Telectronics, the defendant, pursuant to an IDE, began conducting clinical trials of its implantable defibrillator in order to secure pre-market approval for the device. In addition to the sales of the device to clinicians under the IDE, the defendant displayed the device at seven medical conferences to non-physicians. The defendant also promoted the progress of the clinical trials in an effort to raise money from investors. Plaintiff argued that these activities either exceeded the scope of the §271(e)(1) exemption or lost their exemption because the defendant used data from the clinical trials in a manner not reasonably related to obtaining FDA approval. See Telectronics Pacing Sys., Inc., 982 F.2d at 1522-23. In rejecting the plaintiff's claim, the Federal Circuit broke the analysis into two parts. First, the Federal Circuit noted that the plaintiffs admitted that the demonstrations at the medical conferences were not a sale or offer to sell under the statute. The court found in that context, displaying the device as a means of "selecting clinical investigators and providing them necessary information" was an exempt activity.

Id. at 1523. Second, the Federal Circuit found that plaintiffs did not lose their exemption by using data gained from clinical tests for fund raising purposes. The court noted that when it enacted § 271(e)(1), Congress must have been aware of "the need of competitors to raise funds for developing and testing competing products, and for preparing to enter the market once controlling patents had expired." Id. at 15245. Thus, the court concluded, "if Congress intended to make that more difficult, if not impossible, by preventing competitors from using, in an admittedly non-infringing manner, the derived test data for fund-raising and other business purposes, it would have made that intent clear." Id.

In AbTox, Inc. v. Exitron Corp., 122 F.3d 1019 (1997) the Federal Circuit again considered the scope of the § 271(e)(1) exemption. Like in the present case, in AbTox, the defendant contended that it conducted limited tests to collect data necessary for filing an application with the FDA for approval of its device. The plaintiff argued that "the actual purpose of these tests was not to secure FDA approval, but was intended, inter alia, to promote the [device] to potential customers." Id. at 1027. In rejecting the plaintiff's argument, the Federal Circuit stated, the statute "does not look to the underlying purposes or attendant consequences of the activity . . ., as long as the use is reasonably related to FDA approval." Id. at 1030. Further, "as long as the activity is reasonably related to obtaining FDA approval [defendant's] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield." Id. This broad interpretation of the § 271(e)(1) exemption seems to support AmCell's motion for summary judgment.

Plaintiffs contend that these opinions are not binding in this case because the Federal Circuit only considered whether manufacturers could use data gathered in pursuit of regulatory approval for some collateral use. Here, plaintiffs do not contend that defendants are disseminating data as a marketing tool, but rather that defendants have infringed the Civin patents by marketing CliniMACS/CD34 and by pursuing clinicians to participate in clinical investigations that are not necessary to obtain regulatory approval. That is, the plaintiffs claim that the defendants do not need the clinicians to perform all of the investigator-sponsored clinical tests to obtain FDA approval for CliniMACS/CD34. Moreover, plaintiffs question whether defendants' promotional activities are reasonably related to the gathering of the data.

Central to this dispute is whether this court ought to intervene between the defendants and the FDA. That is, if the FDA has not explicitly limited AmCell's communication with clinicians or the scope and type of trials it may use to secure approval for CliniMACS/CD34, is the court in a better position to determine whether AmCell's activities are reasonably related to the development and submission of data to the FDA?

Pursuant to federal law, the FDA establishes regulations to oversee the development and testing of medical devices. The FDA requires manufacturers to test the safety and efficacy of medical devices before bringing the product to the market. The FDA plays an active role in determining the type of information a manufacturer must provide in seeking approval for medical devices. That is, the FDA helps manufacturers

design tests and structure their application for approval. Thus, the FDA is in a better position than the courts to determine what activities are reasonably related to obtaining regulatory approval.

Moreover, the FDA bars manufacturers from transporting or selling devices in interstate commerce that do not have either pre-market approval or an IDE. In doing so, the FDA prohibits a manufacturer or sponsor of an investigational device from promoting, test marketing, commercializing, or unduly prolonging an investigation of a device.[1] See 21 C.F.R. § 812.7. Thus, the FDA is also in a better position than the court to determine what activities are not reasonably related to obtaining regulatory approval.

Nonetheless, plaintiffs contend that the FDA is not concerned with enforcing patent rights and does not have a mechanism to provide relief to a patent holder. The

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[1] The regulation states:

812.7 Prohibition of promotion and other practices.

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

21 C.F.R. § 812.7

court disagrees. Given that the FDA forced AmCell to modify its website and rejected 17 applications for investigator-sponsored IDEs, the court believes that the FDA is concerned with the distinction between the approval process and the promotional process. That is, by controlling a manufacturer's commercial messages and disallowing applications for IDEs where the FDA believed that the trial would not yield useful data or where the manufacturer is promoting, test marketing, commercializing, or unduly prolonging the investigation of a device, the FDA is telling the courts what activities fall within the scope of the § 271(e)(1) exemption. Thus, it is not necessary for the FDA to focus on whether or not something infringes a patent-holder's rights to protect the scope of a patent.

In this case, it appears that the FDA has found that certain activities are reasonably related to obtaining approval and raised with AmCell whether certain other activities are not reasonably related. That is, the FDA has reviewed with AmCell whether some of its activities will provide useful information in support of the application and has considered whether AmCell prematurely promoted the safety and efficacy of its product. The FDA has put AmCell on notice that it will disapprove of certain identified activities and request it refrain from certain conduct. Consequently, as the FDA is in a better position to determine what activities are reasonably related to obtaining approval and as it is doing it in this case, the court will defer at this time to the FDA's judgment on whether AmCell's activities are reasonably related to obtaining approval.

Given these findings, the question is how best to proceed. The parties have presented the issue in the context of cross motions for summary judgment. The court will not resolve the issue of whether the AmCell's activities are protected by § 271(e)(1). Rather, the court will defer to the FDA. The FDA can resolve the issue and define for AmCell what activities are reasonably related to the development and submission of information necessary to obtaining pre-market approval for its device and in doing that, it can also identify what activities are not reasonably related to obtaining approval. If AmCell persists in activity the FDA finds is not reasonably related, Nexell can seek relief from this court, including relief for activities identified in its complaint in this action. Should the FDA decline to identify which of AmCell's activities are not reasonably related to obtaining approval, Nexell can renew its claim for relief.

At this time, the most appropriate resolution is to grant summary judgment to AmCell with the understanding that the judgment will not preclude Nexell from revisiting these issues in the future.

III. CONCLUSION

For the reasons stated above, the court will grant AmCell's motion for partial summary judgment of non-infringement under § 271(e)(1) and deny plaintiffs' cross-motion for partial summary judgement of infringement. The court will enter an order consistent with this opinion.