JOURNAL

of the Association of University Technology Managers™

Volume XVIII Number 2

Fall 2006

Patenting, Licensing, and Social Responsibility

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JOURNAL

of the Association of University Technology Managers™

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Patenting, Licensing, and Social Responsibility

Printed in the USA

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Editor's Preface

Whenever it's time to choose the next theme for an upcoming issue of the *AUTM Journal*, I find myself taking a tiny leap of faith. For, despite the breadth of diversity, industry knowledge and combined experience of the *AUTM Journal* Editorial Advisory Board and editors, selecting a topic that is timely, interesting, and, perhaps most importantly from an editor's point of view, inspirational to potential authors, requires a good deal of deliberation and a dollop of intuition.

So we were more than pleasantly surprised—and maybe even a little overwhelmed—at the response we received from the call for abstracts for this issue, which sought papers on "Patenting, Licensing, and Social Responsibility."

Clearly, if the magnitude of the response is any indication, this important topic resonates throughout the technology transfer community. Perhaps because it is not only a complex and timely subject with great implications within universities but also to people worldwide as they are the potential beneficiaries from discoveries made at nonprofit institutions.

However, while the assuredness of the topic is evident, the mechanics of accomplishing socially responsible patenting and licensing at universities are still under debate. And that is, in part, what this issue of the *AUTM Journal* is all about.

In "Human Embryonic Stem Cells: A Review of the Intellectual Property Landscape," Irene Abrams discusses the complex patenting and licensing world of human embryonic stem cells (hESCs). The paper provides a history on hESCs and outlines the major patents in the hESC field and their availability for licensing in both research and commercial areas. Abrams goes on to describe the intellectual property provisions agreed upon under the recent hESC legislation passed in California and asserts that the intellectual property landscape surrounding hESCs is clearer and licensing is available in most fields.

In the second article, "Technology Licensing for the Benefit of the Developing World: UC Berkeley's Socially Responsible Licensing Program," Carol Mimura, PhD, describes the University of California at Berkeley's Socially Responsible Licensing Program (SRLP). Begun three years ago as a response to faculty member's dengue fever diagnostic, SRLP guides licens-

ing of inventions applicable to nontraditional markets, such as developing countries. Mimura cites examples of Berkeley's contracts signed under SRLP, as well as selected contract clauses and policies. Berkeley also restructured intellectual property management by consolidating industry interactions with the university, thereby streamlining the university-industry interface and measuring success on all interactions with industry, not solely licensing revenue. Mimura cites this view of success as enabling new strategies for intellectual property management, including unique approaches for technologies applicable to needs in developing nations.

The third topical paper, "Parallel Importation: A Threat to Pharmaceutical Innovation?" from Jessica Marter-Kenyon and Jolene Wun, addresses industry's concern of smuggling therapeutic drugs from developing countries to developed countries. In license agreements for global health technologies, some universities are currently considering including clauses requiring the exclusive licensees to grant sublicenses to generic manufacturers for sale of the therapies in developing countries. Industry views parallel importation as a large issue, in part because it could deplete the market value of drugs. After reviewing laws and particular cases, Marter-Kenyon and Wun conclude that parallel importation should not be a large concern to industry with regard to the profitability of the therapies.

Susan Tandan and Rebecca Crane familiarize readers with Canada's recent Jean Chretien Pledge to Africa (JCPA) in their article, "Canada's Helping Hand: Jean Chretien's Pledge to Africa Legislation Allowing Export of Pharmaceuticals under Compulsory License." This unique legislation allows for compulsory licenses for manufacture in Canada of lower-cost versions of patented pharmaceuticals for export to countries unable to manufacture the pharmaceutical themselves. Time will tell if JCPA is effective—although in force more than a year, the Canadian patent office has not received any license applications.

The final topical article, "Surveying the Need for Technology Management for Global Health Training Programs," comes from Usha Balakrishnan, MBA, Lisa Troyer, PhD, and Edwin Brands, PhD. The authors surveyed technology licensing offices regarding their practices with inventions related to global health and determined that technology managers need education to effectively handle global health technologies arising from university research.

The Legalink article in this edition is an opinion paper on the importance of claims in provisional patent applications. In "Why Provisionals Need Claims," Todd Juneau, JD, asserts that, although the rules of the United States Patent and Trademark Office state that provisional patent applications may be filed without claims, the enablement and written description requirements contradict the practice of filing without claims. Juneau provides case examples supporting filing provisional patent applications with claims.

Lastly, Lisa Richter and I would like to extend our heartfelt thanks to Geoff Schmidt—first a member of the *AUTM Journal* Editorial Advisory Board, then associate editor of the *AUTM Journal* since 2005. He has gone above and beyond expectations, and his tremendous contributions, insightful comments, and unique brand of wit will be truly missed. We wish him enormous success in his new venture in cancer diagnosis, which, as reflects the theme of this issue, would greatly benefit all people.

On a happier note, we are very pleased to welcome Afshin Afshari, ing, PhD, MBA of École de technologie supérieure as the incoming associate editor. Afshin brings his many years of *AUTM Journal* Editorial Advisory Board and industry experience, as well as an international perspective, to this volunteer position, and we look forward to working with him in this new capacity.

— Kirsten Leute, Editor
Stanford University

Human Embryonic Stem Cells: A Review of the Intellectual Property Landscape

Irene Abrams

Abstract

It is hard to have missed the controversy surrounding human embryonic stem cell (hESC) research. Researchers who are interested in this field believe that hESCs' potential to cure many previously incurable diseases, such as type 1 diabetes and neurodegenerative disorders, outweigh the concerns raised by critics who object to hESC research because a human embryo is destroyed during the creation of hESC lines. For those who are interested in research on hESCs, there is also a complicated intellectual property landscape to navigate. This paper will review the major patents in the hESC field and their availability for both research and commercial purposes. This paper will also review the recently released intellectual property policy put forth by the State of California that accompanies its funding of stem cell research. California's policies will likely serve as the model for other states' funding of stem cell research. The goal of this paper is to clarify the intellectual property landscape so that researchers and university intellectual property professionals can have a basic understanding of what barriers exist to research and commercialization and how to overcome such barriers in this exciting field. The good news is that, for most uses of hESCs, rights are available through licensing.

Setting the Stage: Some Science and Some History

It is impossible to make sense of the intellectual property landscape surrounding hESCs without first understanding a little about the biology of hESCs and some of the history and politics that have influenced the funding of research on hESCs in the United States.

Irene Abrams is executive director of the Office of Technology Licensing at Brandeis University in Waltham, Massachusetts.

What Are hESCs?

Stem cells are the cells in the body that can divide and produce other types of cells. They serve to build and replenish the body's tissues and organs. They also are able to make every cell type and, therefore, every tissue in the body (this quality is called *pluripotentcy*). They are like the fertilized egg, which is a single cell that gives rise to every cell type in the body. That means that hESCs have the potential to be used to make replacement tissues and organs to cure disease.

Human embryonic stem cells are made from fertilized eggs that have divided a number of times to form a cell mass called a *blastocyst*; hESC lines are derived from single cells that are removed from the blastocyst. This process destroys the blastocyst, which had the potential to develop into a human being. Critics equate this destruction of the blastocyst with the taking of a human life. Proponents counter that the hESC lines that exist have been made from fertilized eggs, left over from in vitro fertilization, that were going to be destroyed anyway. These blastocysts are made outside of the body (in vitro) and are not implanted in a uterus at any time.

There are many types of nonembyronic stem cells called adult stem cells. Adult stem cells exist in many tissues, and they make the cells that tissues use to replenish themselves. For instance, hematopoietic stem cells are cells that produce blood cells. Unlike pluripotent hESCs, adult stem cells are differentiated, which means they can form the cells of certain tissues, but can no longer form all of the cell types of the body. For example, hematopoeitic stem cells can make the various blood cell types, but they cannot make skin. The only currently approved human stem cell therapies use adult stem cells. The most well-known example is bone marrow transplants.

Given this complicated political and moral backdrop, why do researchers want to use hESCs rather than adult stem cells? Many scientists believe that hESCs have the greatest potential for human therapeutics because of their great flexibility to further differentiate into every possible cell type. In addition, it is not clear that adult stem cells exist in all tissues; for example, adult stem cells have not been found in the pancreas.

Funding of hESC Research in the United States

The political history of federal funding of hESC research has shaped the intellectual property landscape. In the United States, the federal government funds almost all of the basic research in the life sciences, mainly through the National Institutes of Health (NIH). From 1980 to 2001, there was a moratorium on federal funding of research on human embryos, which precluded funding of research on hESCs. In the 1990s, political pressure grew from the scientific community and patient advocacy groups to change this rule and to permit funding of research on hESCs. In response to this pressure, President George W. Bush released a policy[1] in 2001 that permits limited federal funding for hESC lines. The limitation was that federal funding could be used only for research on hESC lines in existence at the time the policy was announced. This compromise gave scientists permission to do hESC research, but prohibited federal funding for the creation of or research on new hESC lines. There is no prohibition in the United States on research on hESCs, but without federal funding, the ability of scientists to conduct basic research in this area is severely limited. Basic research on hESCs is continuing outside of the United States in countries that do not have similar restrictions. For example, Great Britain and Israel are emerging as leaders in research on hESCs. Against this political backdrop, some states, such as California, have entered the arena of funding research on hESCs.

Patents on hESCs

The concept that regenerative cells, such as stem cells, exist has been around since the early 1900s, and many different researchers have worked on aspects of understanding stem cells. However, James Thomson, a professor at the University of Wisconsin, was the first to isolate hESCs. As the first to do so, he was awarded a very broad patent, US Patent No. 6,200,806, which issued on March 13, 2001, and is assigned to the Wisconsin Alumni Research Foundation (WARF). A related patent application was filed in Europe and is on appeal in the European Patent Office. There are no related patents pending in Asia, Australia, or Israel.

The patent covers three aspects of hESC: an isolated culture of hESC, the method of isolating hESC cells, and the cell lines derived from such a method. Below is a review of the actual patent claims. This patent is not

limited to any specific tissue types, nor is it limited to any particular use of hESCs, so it could be read to cover every type of hESC, and any research, diagnostic, or therapeutic use of hESCs. In effect, any use of hESCs, of any type, for any purpose, may fall under this patent. This patent, along with two other related Thomson patents, has recently been challenged by two public interest groups in California, the Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation. The groups have filed a request for reexamination of the issued patents with the United States Patent and Trademark Office (USPTO). If the reexamination request is granted, the patent office examines the patent claims again in light of new information. The basis of this challenge is that the discovery was not novel. It is too early to predict whether this challenge is valid or will be successful.

The first claim of this patent is to the actual hESCs themselves, and it is directed toward pluripotent hESCs, which are the kind of hESCs that can turn into any human tissue. The actual claim reads: "Claim 1: A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer."

The next claim of major interest is directed toward the method of isolating hESCs. Claim 9 reads: "Claim 9: A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of (a) isolating a human blastocyst; (b) isolating cells from the inner cell mass of the blastocyst of (a); (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed; (d) dissociating the mass into dissociated cells; (e) replating the dissociated cells on embryonic feeder cells; (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and (g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic hESC line."

And finally, Claim 11 speaks to the cell lines derived from such a method: "Claim 11: A cell line developed by the method of claim 9."

Availability of the Thomson Patent

Thomson is a researcher at University of Wisconsin, and he consequently assigned his rights in this patent to the Wisconsin Alumni Research Foundation (WARF), its technology transfer organization. WARF has formed a subsidiary named the WiCell Research Institute Inc. (WiCell) to handle the licensing of its hESC patents and materials. All licensing is done by WiCell. WiCell licenses both the patent rights and the hESCs developed by Thomson. The hESC lines developed by Thomson were made before Bush's policy on hESCs was released and are, therefore, approved for research using federal funding.

WiCell signed a memorandum of understanding (MOU) with the Public Health Service (PHS), US Department of Health and Human Services, on September 5, 2001, in which WiCell granted rights to PHS-funded researchers (with limitations to be discussed below). PHS includes the NIH, which funds most of the life science research in the United States. The MOU covers access to the hESC lines developed by Thomson (WiCell materials), access to the patent rights for use with the WiCell materials, and for use with other approved hESC lines.

Terms of the MOU: Access to Thomson Patent Rights

The patent rights are available, free of charge, to researchers funded by PHS for use only on hESC lines approved by the government. Such rights are available as well for third-party suppliers of approved hESC lines provided to PHS researchers. In effect, WARF has agreed not to enforce its patent against academic researchers who wish to work on the approved hESCs.[2]

There are some limitations to this grant of rights. The first is that researchers cannot do work for commercial purposes or for the direct benefit of a research sponsor, unless such sponsor has independently received rights from WiCell. Third-party suppliers of hESCs (that is, the owners of the other approved hESC lines) are granted the right, free of charge, to distribute their hESCs to PHS-funded researchers, provided that such suppliers may not directly or indirectly receive intellectual property rights in exchange for the supply of materials. Very importantly, WiCell does not ask for any reach-through rights to discoveries made by academic researchers. Universities are expected to sign a MOU directly with WiCell.[3]

Terms of the MOU: Access to Thomson Cell Lines

The WiCell materials, which are approved under the government's policy for federal funding, are available to PHS-funded researchers for a nominal fee (as of this writing, the fee was $500 per cell line, recently reduced from $5,000). These cell lines come with some restrictions.

The cell lines may not be used for diagnostic or therapeutic purposes and may only be used in noncommercial research, which means they may not be used in industrially sponsored research, unless the industrial sponsor has a separate license from WiCell. There are some restrictions on the use of the cells to prevent the cells from being turned into embryos. Universities are required to certify their compliance with these rules annually, to share the subject of their research, and to share small amounts of new materials, free of charge, with WiCell.

Other Approved hESC Lines

Under the MOU, third-party suppliers of hESCs are granted rights to transfer the materials to PHS-funded researchers, so long as the terms of the transfer are no more onerous than WiCell's terms. That, in effect, has made the terms of the other hESC suppliers nearly identical to WiCell's.[4]

Creation of New hESC Lines

Researchers who wish to create new hESC lines are prohibited from doing so under federal funding and must get funding from other sources, such as companies, foundations, nonfederal government agencies, or private donations. In these cases, the rights to the Thomson patent are not granted under the MOU. Below are the means of access to the Thomson patent for such work.

Commercial Funding

Researchers who wish to work on hESCs under commercial funding can get access to the Thomson patents if the commercial funder obtains rights directly from WiCell. Research-use rights (excluding any preparation for therapeutic use and any diagnostic use) are available for all cell types on a flat-fee basis; the fee is based on company size.

For rights to commercialize hESCs, nonexclusive licenses are available. These are based on applications, i.e., sale for research use, diagnostic or

therapeutic use, and cell type. For diagnostic and therapeutic uses, the important fields of heart, pancreas, and nerve are not available because they are exclusively licensed to Geron (more detail below).

Other Sources of Funding: Foundations, Private Donation, State Funding
Funding for hESC research is available from a number of noncommercial sources such as foundations, private donations, and state governments. Institutions that wish to get access to the patent rights for research in these areas must get the rights directly from WiCell. WiCell has granted a number of such research licenses on terms similar to those in the MOU.

Geron's Rights
Geron funded some of Thomson's work that led to the patents discussed above. As a research funder, Geron was offered an option to a royalty-bearing exclusive license to the patent rights developed under its funding. These are standard terms of industrially funded university research. Through exercising this option, Geron received exclusive rights for diagnostic and therapeutic uses in the fields of heart, pancreas, and nerve. Geron also has nonexclusive rights to a number of other cell types. Geron has the right to sublicense its exclusive rights.[5]

Other Patents on hESCs
Many other researchers and companies other than WARF have been active in the hESC field.[6] The other patents contain limitations that make them less broad in scope than the Thomson patent. For example, Vanderbilt University owns US Patent No. 5,453,357, which claims a composition comprising (a) pluripotential embryonic stem cells and (b) fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor. To fall under the claims of this patent, a product would have to include both the stem cells and the four named components in the media. Similar limitations are common in other hESC patents, such as Geron's patent, US Patent No. 6,642,048, and Amrad Corp. Ltd.'s patent, US Patent No. 5,166,065. The Johns Hopkins University's patent, U.S. Patent No. 6,090,622, is limited to human embryonic germ cells. Other patents, of which there are many, are tissue specific. In conclusion, the other hESC patents are narrower than the WARF patent and so it is possible to

work in the hESC field without needing rights to many of these patents. Of course, a researcher should check whether any particular product, or method, falls under the claims of specific hESC patents.

The Situation in Europe

To date, patents on hESCs are not permitted in Europe. The European Patent Office (EPO) is required to consider moral issues in the granting of patents. In 1999, the European Patent Commission (EPC) adopted a piece of legislation from the EU Biotech Directive in its EPC Implementing Regulations, creating what is called Rule 23d(c)EPC, which reads, "uses of human embryos for industrial or commercial purposes" are to be excluded from patentability. The EPC has interpreted this rule very broadly and has rejected all patents relating to hESCs, including methods of making and using hESCs and products derived from hESCs, such as differentiated cells. The Thomson patent has been rejected on these grounds and is on appeal. It should be noted that some national offices in Europe are taking a narrower view of Rule 23d(c)EPC. The United Kingdom patent office, for example, is granting patents to pluripotent stem cells, but prohibiting patenting of totipotent stem cells and the processes of obtaining hESCs. The German patent office is also taking a narrower view of the EPC ruling. As a strategy, some companies are filing directly in the national offices and bypassing the EPO.

The EPC's refusal to grant patents on hESCs in Europe means that anyone is free to practice any stem cell invention in Europe; however, there is also no market protection for hESC products in Europe. Given the appeals pending for the Thomson and other patents, the situation in Europe will likely change and is worth watching.

Summary of hESC Patents

WARF owns a very broad patent in the field of hESC, potentially dominating both research and therapeutic uses, in all therapeutic fields, using all cell types. For PHS-funded researchers who wish to work on hESCs approved by the federal policy, the patent rights are available, free of charge, through WiCell. For academic researchers who wish to work under commercial sponsorship, to develop new hESC lines, or perform research on nonapproved hESC lines, the commercial sponsor must get the rights from WiCell;

they are available. For academic researchers who wish to use other non-commercial sources of funding to create novel cell types, such as foundations, gifts, or state governments, the rights are available directly from WiCell, subject to negotiation.

For companies that wish to do research on hESCs, the rights are available for a flat fee from WiCell. For companies that wish to commercialize hESCs, the rights are available on a nonexclusive basis from WiCell (terms not publicly available), but the fields of heart, pancreas, and nerve are not available because they are exclusively licensed to Geron, which may or may not be willing to offer a sublicense. This is critical because these hESCs include ones that might lead to regeneration of nerves, cure diabetes, and/or treat heart disease.

For universities that wish to license their hESC patents and are concerned about freedom to operate for their licensees, it appears that there are very few barriers outside the fields Geron has rights to since WiCell is making the rights available to companies.

Other Funding of hESC Research: California

In response to the federal restrictions on funding of hESC research, a number of states have stepped into the void. The first was California. On November 2, 2004, the residents of California passed California Proposition 71, which established the California Institute for Regenerative Medicine (CIRM) to disburse up to $3 billion in state bond funds to conduct hESC research at California universities and institutions and construct research facilities. Many other states have proposed legislation to fund hESC research, including New Jersey and Massachusetts. None yet rival the size or commitment of California.

On February 10, 2006, CIRM released its Intellectual Property Policy for Non-Profit Organizations.[7] This critical document lays the groundwork for how inventions arising from CIRM funding will be handled, and it is likely to be the model that other states follow as they begin funding basic research. Terms for commercial recipients have not yet been released.

CIRM has put together an excellent, well-thought-out, and reasonable intellectual property policy. Its policies will likely encourage the commercialization of hESC research while not putting excessive restrictions on recipient institutions. Like Bayh-Dole, CIRM allows universities to control

the commercialization of inventions made under CIRM funding. Because the policies are compatible with those governing commercialization of federally funded research, universities and other nonprofits will be able to manage the CIRM funding within their existing structures.

CIRM Specifics

Ownership of Intellectual Property

Recipient institutions will own, patent, and be able to grant licenses to inventions made under CIRM funding.

Financial Aspects

CIRM requires that recipient institutions share some of their revenue with the State of California. In particular, for a given invention, for any income more than $500,000 (cumulative), the institution must share 25 percent with CIRM, after the inventor's share is distributed. This allows CIRM to share directly in blockbuster patents, but relieves universities of the burden of sharing revenue from smaller inventions. Interestingly, WARF has interpreted this revenue sharing as commercial use and has approached CIRM to request a share of this revenue as a licensing fee.

Access to Research Result

Recipients are required to share biomedical materials for research purposes in California within sixty days of request (with a few, very limited exceptions).

Exclusive Licensing

The intellectual property policy emphasizes nonexclusive licensing, but recognizes that exclusive licensing is necessary for investment in development and so does not directly discourage it.

Price Controls

Exclusive licensees must plan to provide access to resultant therapeutics and diagnostics for uninsured California patients at federal Medicaid prices.

CIRM Concerns

The policies listed above will allow nonprofits to manage their intellectual property just as they do for federally funded research and industrially funded research. CIRM does not ask for control of intellectual property or control of licensing, nor does it ask for unreasonable financial returns. None of these policies will act to impede commercialization of CIRM-funded research; however, there are a few aspects of the policy that cause concern. These are listed below.

Research Exemption

All California research institutions, both for profit and nonprofit, are granted a research exemption to use any inventions developed under CIRM funding. This means that CIRM-funded inventions cannot be enforced against any California institutions, including companies, using the invention for research purposes. This will surely simplify certain types of research by removing the need for licenses; however, it also precludes market exclusivity for research products and services. There are certain research products and services that need the incentive of market exclusivity to attract investment in product development and marketing. If California becomes a hub for hESC research as a result of CIRM funding, the research exemption may destroy important markets for certain research products and services and will potentially discourage commercialization of an important category of products in the hESC field.

March-in Rights

The State of California has some very broad, and worrisome, march-in rights: "CIRM shall have the right to require the grantee organization, or exclusive licensee…., to grant a nonexclusive, partially exclusive or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable…. if the CIRM determines that such an action is required…." [8]

It can be required if:

1. Grantee organization or licensee has not made responsible efforts in a reasonable time to achieve practical application of a CIRM-funded patented invention

2. Licensee has failed to adhere to the agreed-upon plan for access to resultant therapies
3. To meet requirements for public use when the requirements have not been satisfied
4. To alleviate public health and safety needs which are not reasonably satisfied by the grantee organization or licensee and which needs constitutes a public health emergency

These march-in rights are so broad that it is conceivable that they will discourage investment in important therapeutic products because of the risk of loss of exclusivity after investment. For example, look at reason No. 1: If the licensee has not brought any invention to fruition in a "reasonable time," CIRM can take the rights away. How will a reasonable time be determined for an area as uncertain as hESC therapy? Reason No. 3 is also quite ambiguous. There is no definition of "public use requirement," nor are there examples of what it might mean to say it has not been satisfied. Reason No. 4, "to alleviate public health and safety needs," could easily lead to a situation in which a patient advocacy group demands access to an invention, and the political pressure is such that CIRM agrees and marches in. While such a march-in might (or might not) be the best approach in that individual case, such a use of a march-in will scare off future investors. Such broad march-in rights, held by a state government, might discourage investment in the very inventions they hope to see commercialized. These are extremely high-risk, early-stage investments, and strong market protection will be needed to convince investors to fund such companies and develop hESC therapies. The impact of these march-in rights will hinge on whether they are invoked. If they are not invoked over a long period of time, investors will feel more confident, as they do with federal march-in rights in federally funded inventions, which have never been invoked, and, thus, do not discourage investment.

Aside from these concerns, however, this policy is very good for university technology transfer and development of early-stage research. And, as in many things, California often leads the nation. As more states move into the funding arena, the CIRM policies will serve as a template and will likely benefit recipients of other state funding.

Conclusion

Over time, the intellectual property landscape around hESCs has become clearer. WARF, working with the PHS, has set up a system in which the rights to the Thomson patent are available, via license, in almost all fields with the exception of a few therapeutic areas, for use with government-approved hESC lines and for formation of novel hESC lines. California's funding of stem cell research is moving forward, and its intellectual property policies will make it simple for nonprofits to accept CIRM funding and work within its intellectual property rules. While the future of hESCs as a therapy is still very speculative and actual treatments are far off, the intellectual property situation should not prevent this field from moving forward.

Notes

1. The White House, "Fact Sheet: Embryonic Stem Cell Research," news release, August 9, 2001, http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html.
2. The memorandum of understanding is available for download at http://stemcells.nih.gov/staticresources/research/registry/MTAs/Wicell_MOU.pdf.
3. The memorandum of understanding is available on the WiCell Web site at http://www.wicell.com/.
4. The NIH Web site at http://stemcells.nih.gov/ is an excellent resource to find details of each hESC line (numbered now at about twenty-two) and the details of the availability of each.
5. More information can be found on the Geron Web site at http://www.geron.com.
6. For an excellent review of these patents, see Robert W. Esmond and Robert A. Schwartzman, "Stem Cells: The Patent Landscape," June 2005, http://www.skgf.com/media/news/news.148.PDF.
7. For more information about the Intellectual Property Policy for Non-Profit Organizations, see the Web site at http://www.cirm.ca.gov.

Technology Licensing for the Benefit of the Developing World: UC Berkeley's Socially Responsible Licensing Program

Carol Mimura, PhD

Abstract

In the few decades since passage of the Bayh-Dole Act of 1980, university technology transfer success has been measured primarily by traditional metrics such as numbers of patents filed, revenue obtained from licensed patents, and numbers of startup companies founded to commercialize university intellectual property. Intellectual property (IP) managers have often responded to these metrics and expectations by attempting to maximize revenue from commercial IP licenses. In the last several years, the University of California at Berkeley has acknowledged that, while license revenue generation and local economic development are important goals, it is equally important to maximize the social impact of research and, therefore, adopted several IP management strategies, including a Socially Responsible Licensing Program. Several types of agreements have been executed under SRLP, including IP licenses, sponsored research agreements, and collaborative research agreements. All are structured to provide an economic incentive to licensees to develop and distribute goods and services to low- and middle-income countries and/or to other target groups as they are defined in each contract.

Introduction

Increasingly, university technology transfer programs are becoming aware of the need—and the opportunity—to translate their research findings into solutions not only in their states and nation but also in nontraditional markets such as in developing countries. At the University of California at Berkeley (Berkeley), which has long been associated with progressive social

Carol Mimura, PhD, is assistant vice chancellor for Intellectual Property and Industry Research Alliances at the University of California at Berkeley.

policy and student idealism, this trend manifests in countless ways. Not only have entrepreneurial researchers made their mark in Northern California by nurturing the biotechnology and the information technology industries[1]—two important economic drivers in the state[2]—they did so while upholding the university's mission. This trend is also reflected in its Socially Responsible Licensing Program (SRLP), one intellectual property (IP) management strategy of Berkeley's IP management office.

The SRLP was conceived approximately three years ago and has several goals, to:

- promote widespread availability of healthcare and technologies in the developing world,
- maximize societal impact and public benefit of technologies developed at Berkeley,
- share revenue and/or other benefits with those who collaborate with Berkeley researchers,
- give proper attribution to a resource/material provider or collaborator, and
- stimulate additional investment by others to achieve these goals.

The program seeks to address affordability and accessibility of drugs, therapies, diagnostics, crops, and vaccines to the developing world by stimulating investment where it has been traditionally lacking under profit-motivated business models.

This article describes the motivations for the program, the IP management reorganization that enabled its implementation, some examples of contracts signed in the last three years, and selected contract clauses that implement principles under the program, such as access to and affordability of drugs, diagnostics, or crops.

Origins of the Program

The SRLP was conceived when Eva Harris, a professor at Berkeley's School of Public Health, collaborated with colleagues in the department of Electrical Engineering and Computer Science to invent a handheld micro-electro-mechanical systems (MEMS)-based diagnostic for the diagnosis of dengue fever. Harris knew that the campus licensing office would have to consider a radical (at the time) approach to enable her company, the Sustainable Sciences Institute (SSI), to garner investment for its application

in tropical regions, starting with Nicaragua.[3] Not only was the licensing office excited about providing the framework for investment to occur, but it formalized the concept as a program as it became apparent that many university-generated technologies could be commercialized both for humanitarian purposes and to meet unique business approaches such as those adopted by product development partnerships. Harris provided the moral compass that forged a deal structure,[4] and other campus researchers, including Jay Keasling, later provided additional deal flow within the program.

Intellectual Property Management Restructure

About three years ago, IP management on campus was reorganized to consolidate industry-university contracts in a single unit. The reorganization consolidated IP licensing and industry-sponsored research activities under a single umbrella unit called Intellectual Property and Industry Research Alliances (IPIRA), creating one-stop-shop access for industry to Berkeley's research capabilities and research outcomes.[5] This consolidation of incoming and outgoing industry transactions in one unit solidified the unit's goals as a service organization whose outcomes are realized in many ways and often in other units on campus. Moreover, the consolidation changed the metrics by which success in technology transfer is measured.

For example, success for IPIRA is defined as success in all aspects of industry-university partnerships, including those that are tallied and reported in other campus units such as the development office. This, in turn, enabled an entire spectrum of IP management strategies to be adopted, including those that benefit the developing world.[6] For example, in the current organizational structure, the future grant of a royalty-free license is financially detrimental to the revenue bottom line of the IP licensing office, but since that strategy stimulates net funding, gifts, relationships, and recognition to the campus that far outweigh the licensing revenue forgone, the benefit can be tallied in the social-impact bottom line and also (in some cases) as research revenue in the licensing office's peer division (the Industry Alliances Office). Using the new metrics and double bottom-line accounting, as long as social impact is valued as strongly as other outcomes such as licensing revenue, then licensing revenue is merely one consideration among many when multifaceted business decisions are made. In the

previous structure in which silos of activity fostered more competition than cooperation, the licensing office would not have had strong incentive to grant such a free license because campus benefit would have been realized elsewhere on campus and/or the personnel who executed the transaction would not have been acknowledged as the drivers of an outcome that is realized outside of the technology licensing office. The campus has allowed IPIRA to apportion credit derived from one peer office to another so that a given action in a broad IP management strategy is not taken at the expense of another and is consistent with, not in competition with, the common goal of maintaining research excellence and maximizing research impact.

In the first fiscal year of IPIRA's operation, corporate sponsorship of research nearly tripled on campus. Gift funding to the campus and foundation funding also increased. IPIRA's contributions to these outcomes are both direct and indirect. The figures are cited here not to imply that IPIRA can take credit for the results, but to illustrate that some of the measurable, anticipated campus benefits resulting from IP management reorganization have been realized. Berkeley's reputation in the industry-contracting arena has also improved.[7]

Several types of agreements have been executed under SRLP including IP licenses, sponsored research agreements, and collaborative research agreements. All are structured to provide an economic incentive to licensees to develop and distribute goods and services to low- and middle-income countries and/or to other target groups as they are defined in each contract. One contractual mechanism used to induce such investment under the program is the grant of a low-cost or free commercial IP license to sell products or services in the developing world coupled to corporate and foundation support for research at Berkeley. In this way, sponsored research investment and the humanitarian impact of research are maximized at the expense of potential future IP license revenue. However, future revenue from licensing is never assured, and the opportunity cost in giving up potential future licensing revenue from sales in the developing world is low in comparison to the benefits derived. In addition, there is the basic moral imperative to further humanitarian causes. The program also provides a service to campus researchers who are willing to accept research funding in the near term on the condition that the campus (and they) forgo potential future IP license royalties from sales in the developing world.

Examples of Contracts

Some examples of contracts under SRLP include the following:

- A license to SSI granting royalty-free sales to a handheld MEMS immunodiagnostic assay in predefined countries for as long as SSI retains nonprofit status.
- A research collaboration and revenue-sharing agreement with the Commonwealth of Samoa that provides Berkeley researchers with access to native mamala tree bark, the source of an antiviral compound. If an antiviral therapy is commercialized, net revenue will be shared with the commonwealth and other stakeholders in Samoa (including native healers and villages). Moreover, biological tangible materials such as plasmids and genes will be named "in such a way that the connection of the gene, gene sequence, or gene product to Samoa will be clear to other researchers."[8]
- A license to a nonprofit agricultural biotechnology company to commercialize certain disease-resistant crops on a royalty-free basis in "least developed" predefined geographies.
- A tuberculosis vaccine agreement with a for-profit biotechnology company stating that if a vaccine is invented from company sponsorship of research at Berkeley, vaccine distribution will be royalty free "outside of Europe, North America, Japan, South Korea, and Taiwan."
- A three-party research agreement coupled to two license agreements for development of a malaria therapeutic based on a $42.6 million grant from the Bill and Melinda Gates Foundation.
- A research collaboration agreement through Africa Harvest Biotechnology Foundation International (a Bill and Melinda Gates Foundation grantee) for the development of nutritionally enhanced sorghum seed for royalty-free distribution to areas of need.[9]

Inducing Investment Where Profit Drivers Do Not Exist: Free Licenses Associated with Research Funding

The highest profile transaction in SRLP under this model is a product development partnership (PDP) funded by the Bill and Melinda Gates Foundation to produce a low-cost version of an existing malaria drug. Contracts underlying the PDP consist of:

- A three-party collaboration agreement between the Institute for One World Health (iOWH), a nonprofit pharmaceutical company);

Berkeley; and Amyris Biotechnologies Inc. (Amyris), a Berkeley startup company;

- A license from Berkeley to iOWH to distribute the drug in the developing world; and
- A license from Berkeley to Amyris to provide the drug to iOWH. This license also grants Amyris the right to sell patented compounds in the developed world under royalty-bearing terms, since the compounds have commercial applications in the flavors, fragrances, and energy industries.

Funding under the three-party collaboration agreement is administered by iOWH as the prime Gates Foundation grantee. The iOWH retains $22.6 million to fund regulatory activities and product distribution, but distributes approximately $8 million to Berkeley to perform basic research on E. coli to create the synthetic drug precursor and approximately $12 million to Amyris to fund applied research on the fermentation and chemical steps.

The deal satisfies the mutual goal of producing a low-cost malaria treatment in tropical countries and provides benefits to each participant. All of the parties in the PDP are known, and the terms of future licenses have been agreed to in advance. Uncertainty about future contract terms has thus been eliminated and gaps between developmental stages have been closed.[10] The structure obviates the need to find a way through the traditional valley of death in drug development when basic research at the university only takes a project so far, and translational research in a startup company cannot proceed until enough private funding has been raised. Future transaction costs have thus been eliminated as well.[11]

The Bill and Melinda Gates Foundation has praised the contractual structure underlying this PDP and hopes that the model would be adopted by other universities for their applicable projects.[12]

The malaria drug PDP deal structure has also demonstrated a unique way for a university startup company to obtain early-stage funding from a philanthropic source, in essence bootstrapping via philanthropy.[13] The dual-commercialization-track strategy pursued by Amyris makes it possible for the company, albeit a for-profit startup company, to reduce the technology to practice for a nonprofit end use (sales of malaria drug in developing nations), but then to deploy the same technology to enter commercial markets in the developed world. It is as though the company has the luxury of

having both a non-profit-style research institute that doesn't have to worry about turning a profit but that will generate innovations for the for-profit side of the company to sell with a profit motive.

Selected SRLP Contract Clauses

Research agreements under SRLP necessarily grant rights to IP that has not yet been developed, whereas license agreements grant rights to IP that exists when contracts are drafted and, therefore, can be analyzed. Contract clauses in research agreements necessarily differ from those in license agreements.

Research Agreements

A research agreement contemplates the future grant of a license to the sponsor to IP that is expected be developed under research described in a written scope of work and its corresponding budget. Such agreements prospectively describe the terms of a future grant of rights to IP that is expected to be developed under the agreement. Therefore, grant clauses are qualified with phrases such as "to the extent that we are legally able to do so" and/or "if all of the inventors concur with the terms." The former phrase, "to the extent that we are legally able to do so," is necessary to address, for example, IP developed through acts in a research program that—despite the expectations of the parties—incur obligations to a third party. Such obligations can arise, for example, if IP incorporates material received under a material transfer agreement from a third party or through collaboration with an outside entity. Similarly, a second sponsor (such as the federal government) could have IP rights if the laboratory research utilizes more than one source of funding. Such encumbrances to the IP are not expected to arise, and consummate laboratory management is required to prevent them, but they cannot be dismissed as a possibility. The latter phrase, "if all of the inventors concur with the terms," addresses the reality that inventorship is a legal determination that can only be made when patent claims are drafted. At that time, it is possible that a researcher will be named an inventor who has not pre-agreed in writing to the grant of special IP terms in a contract. The contracting office can obtain approval from all contemplated inventors, but the unanticipated, future inventor (such a colleague who contributes through a hallway conversation) is the subject of this clause.

Similarly, the manner in which IP rights will be conveyed in the future

has been addressed in a collaboration agreement by stating that Berkeley will make "reasonable efforts to license resultant IP for public benefit, keeping in mind Berkeley's and the sponsor's mutual goals of providing low-cost therapies for free, at cost, or at minimal profit in the developing world."

Sister institutions are invited to join in the development of appropriate contract clauses to further the goals of the program and those of others where IP and other research outcomes can be deployed for humanitarian purposes in developing nations.

License Agreements

In SRLP, commercial license agreements that convey rights to preexisting IP define geographies and/or a field of use and typically grant either a royalty-free right to sell products and/or services or the right to sell at the cost of manufacture and distribution without paying running royalties. To address the situation that a given transaction has been crafted with the understanding that the licensee shares SRLP's goal of deploying rights developed at the university for humanitarian purposes and to reflect the context in which SRLP performed a legal and policy review of a given transaction, the agreement qualifies a given license grant to be in effect "for as long as the licensee retains its nonprofit status."

Legal and Policy Issues

The program utilizes contractual approaches that deploy Berkeley technologies to induce investment where is it needed. Contracting under PDP structures, such as the malaria therapeutic example, is driven by the nonprofit mission of the ultimate vendor and the humanitarian goals of its sponsors. In the for-profit world, corporate constraints are different. Advance contractual mechanisms that address affordable pricing and widespread access have been tried and abandoned in the past (such as CRADA clauses from the early 1990s), and barriers to market entry that go beyond pricing, such as regulatory hurdles in Africa, parallel importation, protection of brand identity when generics are introduced, and insurance, are equally massive obstacles for drug manufacturers to overcome. However, the creation of a foundation structure as a vehicle through which a for-profit company administers its charitable goals while shielding (and keeping distinct) its profit-driven core business may allow drug manufacturers to

take more risks and/or to entertain more controls from public-sector IP owner licensees in SRLP contracts.

Antitrust implications must be considered in all SRLP agreements when the parties agree in advance to a given price, even when that price is set at zero. Certain SRLP license agreements require one or more companies to sell a drug at cost or at the mere cost of manufacture and distribution in the developing world, but the procompetitive aspects of providing a new technology to the needy where they would not otherwise have broad access to such new technology far outweighs the anticompetitive initial appearance based upon developed-world norms. The licenses that grant rights in developed countries follow the "normal" approach of royalty-bearing sales based upon business decisions of the licensees.

One research collaboration agreement under the program implements two goals of the SRLP. The programmatic goals of revenue sharing with a collaborator and ensuring proper attribution of a resource provider or a collaborator are addressed in a contract that facilitates the isolation and characterization of an antiviral compound from the mamala tree, which is indigenous to Samoa. In this contract, Berkeley agreed to share 50 percent of net revenue with the Commonwealth of Samoa and other stakeholders in Samoa if a drug from the research is commercialized. Shared revenue under this agreement is administered through a foundation. The commitment to share future net revenue in this agreement imposes a duty on the university and its researchers to use nonfederal sources of funding for the project because inventions made with federal funding must be distributed according to the Bayh-Dole Act, which stipulates that resultant net revenue must be used for education and research purposes. While the Commonwealth of Samoa and other recipients might well use their share for education and research purposes, that use was not explicitly stated in the contract. In the agreement, Berkeley also agreed to give attribution to Samoan experts, villages, and other collaborators by naming plasmids to reflect the preexisting expertise and origin of the biological starting material and to acknowledge the collaborative nature of the research.

Written Consent

All researchers whose IP rights are affected by contract terms under the SRLP participate in the program on a voluntary basis, in accordance with the University of California's principle of informed participation. The researchers or inventors are apprised of the humanitarian goals of the contracts, and their written consent to the terms is obtained before any transaction is consummated in which, for example, a royalty-free commercial license is either granted outright or promised in the future or when future revenue will be distributed in a nonstandard manner. Technologies and/or research programs that could further the goals of the SRLP are managed under the program only after consultation with the researchers or inventors and corporate partners, and there is no absolute requirement of research programs that might contribute to the goals of the program to include concessions for humanitarian use in developing nations.

Preserving Access

Most technology transfer from universities and research institutes occurs in traditional ways: through teaching, publications, and other forms of information dissemination; consulting; training of students; and interactions with the private sector. Only a small percentage of a university's collective intellectual output is ever made proprietary through IP protection. Therefore, when SRLP makes its results proprietary by patenting, as IP managers, we must demonstrate good stewardship of the IP rights.

Good stewards of IP rights take care to protect public sector access to research tools for research purposes, and a non-negotiable reservation-of-rights clause is appropriate in this program, as it is when licensing any publicly developed IP right. All IP licenses both inside and outside of the SRLP reserve the right for the university and others in the nonprofit sector to use the licensed IP rights for education and research purposes (and also a right to transfer tangible materials that are required to practice a given invention to nonprofit institutions for the same purpose).

Certainly the strategy of not obtaining IP rights at all, or only in certain geographies, is a mechanism for ensuring access when IP rights are not required as a commercialization incentive. A related strategy is to obtain IP rights but then to grant licenses under open access principles[14] and open licenses.[15] Open innovation in the Intel lab near Berkeley, which operates

under an open collaboration agreement with Berkeley, illustrates the kind of innovation acceleration that is encouraged when IP rights are not contemplated, expected to be rare, and/or ancillary to the research.[16]

License restrictions that grant rights only in a defined field of use can also preserve access. For example, a license granting the right to use a gene sequence for a diagnostic test in one format, such as on a high-density nucleotide array (a gene chip) leaves open the possibility of relicensing that same gene to another company for development into a different diagnostic test.

Nonexclusive licensing is another strategy that can preserve access, but licensees in the biotechnology and pharmaceutical industries often insist on exclusive grants as a condition of investing in costly and lengthy research and development that is required to bring a licensed right to the point of practical application. Mandatory sublicensing clauses in many exclusive licenses from Berkeley since 1998 address the situation where the grant of an exclusive license to a licensee allows future applications of the same technology to be developed, not blocked, by the exclusive licensee. Unmet market needs are addressed through this mechanism by requiring the exclusive licensee either to develop a given new application of the licensed right or to grant a sublicense to a third party who will do so.

If an exclusive licensee does not or cannot provide a drug in an area with an unmet need, a more aggressive reserved right of the university would be to a right to re-license the IP rights to a drug generics manufacturer for the purpose of providing access to such country or region. If the SRLP licensee does not provide the drug for a certain market niche, then there should be a mechanism whereby another provider can serve that market. Unfortunately, this specific enhanced reserved right has not yet been successfully incorporated into an agreement (even though more general mandatory sublicensing clauses have been incorporated into patent license agreements at Berkeley for a number of years). We have been testing such an enhanced clause for acceptability and welcome input from potential licensees. We know that parallel importation, brand preservation, product packaging, and the quality of generic drugs are enormous concerns to for-profit licensees. We welcome a dialogue with biotechnology companies and pharmaceutical companies on appropriate text in a given agreement to further promote drug access and affordability and how we might further segment rights within countries such as Brazil, for example, where there are

many poor, but also significant numbers of middle-class consumers who can afford to pay for drugs. Gilead Sciences Inc. deserves credit for leading by example in this regard, as its Access Program demonstrates the company's commitment to providing HIV/AIDS therapeutics to sufferers in areas of significant unmet need.[17]

Conclusion

In the few decades since passage of the Bayh-Dole Act of 1980, university technology transfer success has been measured primarily by traditional metrics such as numbers of patents filed, revenue obtained from licensed patents, and numbers of startup companies founded to commercialize university IP. Intellectual property managers have often responded to these metrics and expectations by attempting to maximize revenue from commercial IP licenses.[18] In the last several years, Berkeley campus administration has acknowledged that, while license revenue generation and local economic development are important goals of the program, it is equally as important to maximize the social impact of research. The technology transfer program spins off and welcomes partnerships with startup companies, does not value overprotection of research outcomes. The SRLP embraces the sentiment of Mary Sue Coleman of the University of Michigan who stated at the 2005 AUTM Annual Meeting℠, "First and foremost, technology transfer must serve our core mission: sharing ideas and innovations in the service of society's well-being."

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Parallel Importation: A Threat to Pharmaceutical Innovation?

Jessica Marter-Kenyon and Jolene Wun

Abstract

While increasing access to medicines is crucial for the welfare of developing countries, it might also increase opportunities for the smuggling of these therapies into the developed world and threaten future incentives for pharmaceutical innovation. This paper assesses the threat by profiling current levels of parallel importation (PI) in two important markets for the pharmaceutical industry: the United States and the European Union. We find that PI is not likely to significantly undermine total profits and should not be a main concern when considering the impacts of open licensing in developing areas.

Introduction

Lack of access to medicines in developing countries is a pressing public health issue. The statistics are bleak: the World Health Organization estimates that one-third of the world's population lacks regular access to essential medicines.[1] However, given the importance of universities in developing life-saving medicines, university technology transfer offices have the opportunity to partially alleviate this problem by including clauses in university-industry licenses that allow for generic production of medicines in low- and middle-income countries.[2] This, in turn, could considerably reduce the cost of these therapies and make them more affordable for the global poor.

A main concern with this type of open licensing is the issue of parallel importation (PI), which is the importation of goods patented in the incoming country without the authorization of the patent holder. Universities conducting licensing deals with biotech companies must remain informed of the

Jessica Marter-Kenyon is a fourth-year undergraduate majoring in development studies at the University of California at Berkeley. Jolene Wun holds a bachelor s degree in economics and development studies from the University of California at Berkeley. *The authors received a research stipend from Universities Allied for Essential Medicines and the Berkeley Center for Law and Technology.*

issues surrounding PI because a main objection to increasing access to technologies is concern over the negative financial effects of PI. Open licensing could potentially create an incentive to import these low-cost drugs from low-income areas to the developed world. Because high-income countries are the overwhelming source of pharmaceutical profits,[3] wide-scale importation could drastically reduce financial gains for both pharmaceutical companies and universities that license these drugs and, thus, hamper the incentive for innovation. This article seeks to determine the size of the threat of PI and to suggest how university technology transfer offices should approach this threat. "Current Opportunities for Parallel Importation" assesses the current price differentials in different parts of the world that may encourage PI. "Illegal Importation of Pharmaceuticals—the Case of the United States" analyzes the current state of illegal pharmaceutical importation in the United States. "Legalized Parallel Importation—the European Union" analyzes the system of PI in the European Union, which practices the principle of regional exhaustion, and the potential for illegal importation. Finally, "Approaches to Mitigate the Potential Effects of Parallel Importation" suggests ways in which governments and pharmaceutical companies can further reduce the threat of parallel importation.

Current Opportunities for Parallel Importation

There are several bases for the international price variations that spur the PI of pharmaceuticals into developed countries. The most obvious and easily documented reason is that some countries, such as Canada, Italy, and Spain, impose price controls of varying degrees.[4] One would expect PI to occur between the United States, where there are no price controls, and Canada. Tiered pricing schemes, or differential pricing implemented by pharmaceutical companies based on the willingness to pay of different countries, also create price differences that may induce PI. Various studies have found that there is a mild positive correlation between drug prices and per capita gross domestic product.[5] Another reason for price differentials, although rare, is the absence of a patent system or governments issuing compulsory licenses for certain pharmaceuticals, resulting in generic production and heightened competition. An example of the former is India, where brand-name pharmaceutical prices were strikingly low prior to the enactment of pharmaceutical patents in 2005, due to high levels of generic

production and competition.[6] Finally, major pharmaceutical companies have voluntarily reduced prices or provided free medications to particularly poor regions of the world.[7] Thus, there is considerable incentive, and, theoretically ample opportunity, for illegal importation of medicines from the developing world into the developed world. Whether this actually happens on a large scale is the subject of the next two sections.

Illegal Importation of Pharmaceuticals—the Case of the United States

The Legal Environment in the United States

In the United States, it is illegal for an entity that does not have permission from the patent holder to import a drug under US patent. This means the United States follows a regime of national exhaustion, whereby the right of a purchaser of a patented product to resell that product is exhausted outside of the nation the product is purchased in. This makes PI illegal.[8]

Drugs marketed in the United States must be produced in plants and bear product labels that are approved by the US Food and Drug Administration (FDA). An exception to this rule is the personal-use policy used by the FDA since 1954, which allows importation of drugs if the product is for personal use and not for resale.[9] The result is a strict ban on mass importation of drugs for the purpose of commercialization, but more ambiguous rules regarding personal imports. Instances of widespread illegal distribution of imported therapies are largely unheard of, while the issue of importing drugs from Canada into the United States for personal use is a highly contentious and widely publicized affair.[10] This ambiguous atmosphere has enabled state and local governments to advocate importing Canadian pharmaceuticals for personal use: states such as Illinois, Iowa, and Minnesota have investigated the potential benefits of drug importation[11] and trips to Canadian pharmacies have been organized by members of Congress.[12]

Case Studies of Illegal Importation

Despite concerns raised over the issue of illegal pharmaceutical importation, there has been little actual in-depth analysis of it. For example, one study published by the US Department of Health and Human Services (HHS)

describes the several avenues through which drugs are illegally imported, such as Internet pharmacies, traveling across the border, and purchasing through third parties.[13] However, it provides little information about who buys the drugs, what types of drugs are purchased, and the volume of sales. HHS cites one study carried out by the FDA, which examined incoming packages at an international mail facility in California. It concluded that about 10 million packages containing pharmaceuticals enter the United States through the mail annually,[14] but did not specify the types of medicines involved or the total value. Another study cited within the HHS report conducted surveys with people crossing the United States-Mexico border and found that the majority of pharmaceuticals transported over the border were antibiotics or painkillers.[15] However, there was no information regarding what percentage of people crossing the border were importing drugs or the estimated volume, nor did the report cite how many drugs were under US patent at the time or what percentage were available in the United States. The report estimated that the value of illegally imported drugs from outside of Canada was $695 million,[16] but it is unclear how it arrived at that conclusion. Since the study, IMS Health, a healthcare consulting group, has estimated that monthly pharmaceutical sales across the United States-Canada border peaked at $43.5 million in 2004, but decreased to $29.6 million in June 2005.[17] One independent consultant estimated that sales have further fallen 20 percent to 30 percent since then, partially due to the increase in prescription medicine coverage under Medicare.[18] Again, however, there was no mention of methodology.

Assessment of Data

The present information is not enough to make a definitive conclusion about the exact threat of illegal importation of drugs into the United States, which is the most lucrative market for pharmaceuticals in the world and the one most pertinent to industry-university licensing deals. Although the studies provide some insight into how many total pharmaceuticals are imported for personal use, they fail to distinguish between (1) drugs that are parallel imports, (2) medicines not available at all in the United States, or (3) medicines whose patents have expired in the United States. The latter two are examples of drugs that are not a large threat to brand-name pharmaceutical companies' profits and, thus, should not be included in our assessment.

Caveats notwithstanding, the total value of imports estimated by IMS Health and HHS ($1.4 billion in 2003) are small when compared to total pharmaceutical industry profits. That same year, GlaxoSmithKline turned a gross profit of £17.2 billion[19] ($30.7 billion[20]). One year later, in 2004, total sales for the entire pharmaceutical industry amounted to $235.4 billion.[21] Thus, PI does not currently appear to significantly affect pharmaceutical profits in the United States and, thus, is unlikely to reduce royalty payments accruing to universities.

We now turn to the European Union (EU), another major source of pharmaceutical revenue, to assess the threat of PI there.

Part III: Legalized Parallel Importation—the European Union

Overview of Legality

The European Union (EU) is the second largest pharmaceutical market in the world.[22] Studying the state of PI within European borders, then, can help technology transfer offices to understand potential consequences of such activity in the United States. The economic and political climate surrounding PI within the EU differs drastically from that in the United States. Under European law, PI is permitted between member states. This allows importation between countries with low pharmaceutical prices and those states with comparatively high prices—provided the drug is identical. Under European law, *identical* denotes drugs containing the same ingredient and having been produced by the same manufacturer.[23] PI of pharmaceuticals begins primarily in such countries as Greece, Spain, and Portugal and ends in the United Kingdom, Germany, and Sweden, the latter three of which have higher pharmaceutical prices than the former.[24] The debate over this stems from the direct conflict between the European principles of free movement of goods, outlined in article 28 of the EU treaty, and member states' rights to domestically govern ownership of intellectual property.[25] Article 28 upholds the principle of regional exhaustion, so EU member states may not prohibit a product from being resold in other states once it has been put on the market in one member state.[26] The European Court of Justice (ECJ) has consistently ruled in favor of article 28 and the principle of free movement of goods, thus upholding the legality of PI within the EU.[27] The potential savings for government healthcare systems has caused some

states to promote PI of pharmaceuticals through government-approved incentives for pharmacies, hospitals, and other healthcare providers that purchase and distribute brand-name drugs brought into their country through PI and penalties for those that do not.[28]

There are limitations on commercial pharmaceutical trade within the EU, notwithstanding the basic regulations pertaining to identical products. Importation of pharmaceuticals is allowed only for licensed distributors; this enables enforcement agencies to better track the flow of products into and out of a specific country. The distributors must also abide by European and national regulations. Drug manufacturers can block the sale of their product if the packaging has been unduly altered. They can also manage their inventories to obtain greater control of supply within a country, so long as they do not explicitly ban exports of their products to other member states. Finally, states can prohibit or limit exports if they are determined to be a public health or human safety concern.

The Scope and Effects of Legal and Illegal Parallel Importation in the European Union

Given that PI has been legalized by the EU, it is useful to discuss the extent to which legal and illegal PI occurs there. First, as opposed to the United States where demand is consumer-driven because of the high cost of pharmaceuticals, PI in the EU is motivated by the opportunity for parallel distributors to profit from the difference in drug pricing among European member states.[29] Parallel exportation is a considerable industry in Europe. For example, it represented more than one-fifth of the Greek market from 2000-2002.[30] Its complement, PI is a similarly large industry. In some EU countries with high drug prices, PI accounts for up to 20 percent of total brand-name drug sales.[31] In 2002, the industry estimated that it lost up to $3 billion per year because of PI of pharmaceuticals.[32] Econometric analyses of price competition in Sweden between 1994 and 1999 suggest that drugs subject to competition with parallel imports generally experience a drop in price, a reduction estimated to be between 12 percent and 19 percent.[33]

Analysis of the extent of illegal importation within the EU can facilitate determination of how illegal PI might affect the US market. Gray-market trade, defined as importation through unauthorized channels, is generally limited in the EU.[34] Goods distributed through gray channels are not in

themselves illegal or dangerous. The gray market refers not to illegally manufactured drugs but rather to the illegal distribution of drugs imported by distributors who have not received authorization to sell from the manufacturer or trade in pharmaceuticals from outside of the EU.[35] The ECJ has severely limited gray imports into the EU, and gray market traders are no longer allowed to undercut the prices of brand-name drugs.[36] Gray import sales ranged, in the mid-1990s, between 2 percent and 10 percent of the total market for prescription drugs in the EU.[37]

Some of the primary fears regarding the potential negative effects of PI should be allayed by Europe's experience with PI. Although legalized importation of pharmaceuticals may undercut prices, the impact of *illegal* importation seems to be minimal. No documented cases of counterfeit drug importation have, as of yet, been attributed to parallel trade.[38] This could be related to the complex trade rules of the EU or to border control. There has also been no recording of drug shortages in the exporting countries.[39] There is, however, concern over "free riding" of gray market distributors off of the research and development (R&D) expended by the original manufacturers. To combat this, European companies can use contracts between the manufacturers and the distributors that provide for a sharing of the advertising costs. The impacts of PI on pharmaceutical R&D spending in Europe have not been conclusively determined.[40] In Europe, the savings from parallel pharmaceutical trade appear to primarily be passed on to the distributors and not to the consumers or the health financing system.[41] Although this may seem to be a blow to proponents of parallel trade, this deficiency in benefits could be partially attributed to the fact that health care in Europe is often state-sponsored and relatively inexpensive in comparison to drug prices in other developed areas of the world. The small nature of the savings European consumers accrue through PI is, thus, due to the fact that they already have fairly inexpensive access to medicines.

Lessons Learned from the European Experience of Parallel Importation

The European phenomenon of legalized parallel trade in pharmaceuticals demonstrates several key lessons about the effects PI could have in the United States. First, we must consider that the EU allows legal parallel importation, a policy that the United States would most likely not adopt. Thus, although PI has affected European pharmaceutical prices, we cannot

necessarily apply this result to the United States' markets. Rather, it is the extent of illegal PI that presents us with the true possibility to estimate the impact PI could have on the US pharmaceutical market. The low incidence of illegal or gray market importation in Europe indicates that the specific EU regulations regarding PI appear to be functioning adequately. This provides hope that the United States would experience similarly low levels of illegal importation were the country to adopt similar enforcement policies and delineated regulations on illegal PI. The United States also has stricter border control and law enforcement procedures with its neighbors than the EU does between its member states, which must allow for the free movement of goods. Since the EU is an economic community with open borders, whereas the United States is an economically sovereign entity, the smuggling of pharmaceuticals should be more easily facilitated between member states in the EU than it would be from Mexico and Canada to the United States. Careful product labeling of imported pharmaceuticals is essential. Consumers are then better informed of the origins and legality of the drug they are purchasing.

Approaches to Mitigate the Potential Effects of Parallel Importation

The European Union's experience with PI indicates that the legalization of parallel pharmaceutical trade allows for regulation of a market that can be quite beneficial for those countries involved. Although current levels of PI are probably low, the possible increase in PI resulting from open licensing can be mitigated through several methods. First, stricter law enforcement and legislation are necessary to both deter and identify illegal distributors. Legislation forbidding state and local governments' complicity in personal importation schemes can facilitate cooperation between lawmakers and law enforcement agencies and assist in impeding illegal importation of pharmaceuticals. Requirements for differentiated packaging of generic products that clearly identify the country of origin of the drug, its contents, and the name of the manufacturer allow for both enforcement groups and consumers to discriminate between American brand-name pharmaceuticals and those that may have been imported from elsewhere. Consumer perception is also vital to combat the sale of gray- and black-market drugs. By and large, people already prefer to buy their pharmaceuticals from well-known brand-name companies and may not buy from gray-market distribution

channels they are unfamiliar with or perceive as hazardous.[42] Governments can also exert influence upon public perception and access to pharmaceuticals that have been distributed in their country through channels of PI. Governmental influence can be applied through the use of public service announcements and education campaigns encouraging consumers to remain aware of the origins of their medications. Drug regulatory agencies such as the FDA occupy a crucial position in terms of regulating the extent of pharmaceutical arbitrage into the United States and controlling consumer perceptions. Doctors, pharmacists, and other members of the health-care sector can also play an important role in maintaining the purchase of American pharmaceuticals by prescribing and promoting non-gray-market medication.

Conclusion

As we have demonstrated, illegal PI does not currently appear to significantly undermine pharmaceutical profits in the two largest markets for drugs in the world: the United States and the EU. This is not to say that illegal PI does not occur at all; however, when we consider that improving access to essential medicines is estimated to save 10 million lives per year,[43] the potential social benefits from allowing generic drug production in the developing world probably outweigh the costs of the increase in PI.

As universities transition toward making their technology available not only to industry, but also for humanitarian causes, they will face PI as a major concern of their licensees. The data and suggestions presented above seek to inform technology transfer directors about the true nature of PI and suggest ways that the system can evolve to combat the potential loss of profits from such importation. PI appears to be a negligible threat to the sustainability of university research and innovation, and, thus, university technology transfer offices do not have a difficult choice to make when deciding whether or not to push for open licensing of their life-saving therapies.

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Canada's Helping Hand: Jean Chretien's Pledge to Africa Legislation Allowing Export of Pharmaceuticals under Compulsory License

Susan Tandan and Rebecca Crane

Abstract

Many developing and least-developed countries are faced with a desperate health situation that cannot be readily solved. Meanwhile, in the developed world, in its quest for a more global economy, the World Trade Organization (WTO) introduced Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 1994, an agreement by which nontariff barriers to trade were removed by increasing intellectual property protection in those regions of the world in which inadequate protection existed. The subsequent Doha Declaration and August 30, 2003, WTO decision were introduced to reaffirm the ability of WTO countries to use compulsory licensing as a means to address public health crises in developing and least-developed countries.

Canada has taken a leadership role with the passage into law of the Jean Chrétien Pledge to Africa (JCPA), which amended both the Patent Act and the Food and Drug Act, permitting the granting of compulsory licenses to manufacture in Canada lower-cost versions of patented pharmaceuticals for export to countries unable to manufacture the pharmaceutical themselves. Although Canada's intentions by implementing JCPA reflect a socially responsible act, the effectiveness of JCPA for its intended purpose has yet to be determined.

Introduction

Developing and least-developed countries, including most countries in Africa, are faced with a desperate health situation. Every year millions of people in Africa are infected with malaria, HIV, tuberculosis (TB), and other debilitating infectious diseases. Several millions of these, particularly

Susan Tandan is a registered Canadian and US patent agent and partner with Gowling Lafleur Henderson LLP, in Hamilton, Ontario. Rebecca Crane was an articling student with the firm at the time of writing.

children, eventually succumb and die. In addition to this huge amount of human suffering and loss of life, infectious diseases impose a heavy economic burden on the already impoverished continent.

At the same time, in the developed world, the vision of globalization gains momentum. In the quest for a more global economy, the World Trade Organization (WTO) introduced the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement in 1994. The purpose of the TRIPS agreement was to remove nontariff barriers to trade by increasing intellectual property protection for many technologies, including biotechnology and pharmaceutical technologies. In response to the subsequent outcry, particularly from developing and least-developed countries on which TRIPS had the greatest impact, the Doha Declaration was introduced, followed by the subsequent August 30, 2003, decision of the WTO which reaffirmed the ability of WTO countries to use various approaches, such as compulsory licensing, as a means to gain access to lower cost versions of patented pharmaceuticals.

As a result of the WTO's sanction of compulsory licensing as well as pressure exerted by civil society organizations, Canada recently amended its Patent Act by the implementation of Jean Chrétien Pledge to Africa (JCPA). The JCPA came into force on May 14, 2005, with the aim of allowing the export of lower cost generic versions of drugs to eligible countries, including developing and least-developed countries. By implementing JCPA, Canada is viewed as taking the forefront in seeking to address the public health crisis of developing and least-developed countries. Indeed, the Canadian HIV/AIDS Legal Network hailed JCPA as being "one important initiative in the larger struggle to increase access to more affordable medicines in the many parts of the developing world where they are desperately needed."[1]

While, in theory, JCPA represents a socially responsible endeavor by Canada, the question remains as to whether it will actually provide an effective means to address the needs of developing/least-developed countries. Against this backdrop, this paper provides an examination of JCPA and the difficulties associated with such legislation in Canada.

TRIPS Agreement

The TRIPS agreement, which came into effect on January 1, 1995, is a comprehensive agreement on intellectual property rights between member coun-

tries including Canada. It essentially requires that WTO members provide strong intellectual property rights, for example, patent protection, in all fields of technology.[2] With respect to patents, the TRIPS agreement provides a general obligation to comply with the substantive provisions of the Paris Convention (1967). In addition, the agreement requires that a twenty-year term of patent protection be available for all inventions, whether products or processes, in almost all fields of technology, subject to the normal tests for patentability. The TRIPS agreement is termed a minimum standards agreement and, as such, it allows member countries to provide more extensive protection of intellectual property if they so desire.

Countries most affected by TRIPS are those in which minimal patent protection existed for the targeted technologies, particularly biotechnology and pharmaceutical technologies. Not surprisingly, these regions comprised, for the most part, developing and least-developed countries. With the requirement to introduce patents for pharmaceuticals, TRIPS has been viewed as a grave obstacle to lower cost generic versions of patented pharmaceuticals by the developing and least-developed world. In addition, the generic pharmaceutical industry that has developed in some of these countries, such as India, and which has helped to supply low-cost pharmaceuticals to neighboring developing and least-developed countries, may also be affected by TRIPS. Thus, with the introduction of broader patent protection in accordance with TRIPS, both countries requiring and supplying low-cost pharmaceuticals may be affected.

TRIPS does provide patentees with the right to assign, transfer, or license their rights. Compulsory licensing is permitted under article 31 of TRIPS. However, article 31 sets out several conditions that must be respected by a member country allowing compulsory licenses. For example, TRIPS provides that the license must be used predominately in the domestic market of the country authorizing the use rather than for export. This condition was perceived by many as unduly restrictive particularly for developing and least-developed countries in light of the fact that most of these countries do not have the capacity to domestically manufacture pharmaceutical products. In response to this concern, the Doha Declaration was adopted in November 2001. The Doha Declaration re-affirmed TRIPS, but also emphasized the need to implement and interpret TRIPS as a means to protect public health by promoting access to medicines.[3] Yet, the Doha

Declaration did not specifically provide for any new exceptions or changes to the existing rules on compulsory licensing in TRIPS. As a result of further negotiation, in a WTO decision rendered on August 30, 2003, member countries agreed that the limitation to the use of compulsory licensing for domestic use only could be waived on an interim basis so as to allow any member country to manufacture for export pharmaceutical products made under compulsory license provided certain conditions were met.

Compulsory Licensing in Canada

Canada was the first to respond to the Doha Declaration and the following August 30, 2003, decision with the passage into law of JCPA, which amended the Patent Act and the Food and Drug Act. JCPA permits the granting of compulsory licenses to manufacture in Canada and export lower cost versions of patented pharmaceuticals to countries in need that are unable to manufacture the required pharmaceuticals themselves.

Compulsory licensing is not new to Canada. Compulsory licensing for patented foods and medicines was introduced into Canada's Patent Act in 1923. In relation to patented medicines, the 1923 amendment allowed a compulsory license to be granted for manufacture of a medicine in Canada. In 1969, amendments to the Patent Act further allowed for a compulsory license to be granted for the importation of patented medicines. However, in 1987, the compulsory licensing system in Canada was significantly altered by the implementation of bill C-22, which provided a specific fixed period of patent protection for patented medicines before a compulsory license could be granted. In addition, the 1987 amendments to the Patent Act created the Patented Medicine Prices Review Board to monitor and control the prices of patented medicines. In 1993, the Patent Act was again amended to implement TRIPS and North America Free Trade Agreement provisions on intellectual property. It was through these amendments that compulsory licensing in Canada was eliminated. With the passage of JCPA, compulsory licensing has been re-introduced into Canada, albeit under limited terms.

The Jean Chrétien Pledge to Africa

JCPA came into force on May 14, 2005, with the objective of facilitating the access of pharmaceutical products to eligible developing and least-developed countries. Under these new amendments to the Patent Act, the

Canadian Patent Office may authorize an applicant to make and use a patented invention for purposes directly related to the manufacture of a pharmaceutical product for export to eligible countries.

The Patent Act identifies countries, both WTO and non-WTO countries, that are eligible to receive a pharmaceutical product exported from Canada under JCPA. JCPA, thus, recognizes the need of non-WTO member countries to have access to pharmaceutical products by importation. To effectively address the continuing needs of developing and least-developed countries, countries may be added to the list of eligible countries. Non-WTO, least-developed countries are automatically added to the list of eligible countries, while non-WTO developing countries may be added to the list on request if they are recognized by the Organization for Economic Cooperation and Development as eligible for official development assistance.

To access an importing license under JCPA, an eligible country must

1) publicly identify the pharmaceutical and the quantity it requires;
2) indicate that it will be issuing a compulsory licence to import the pharmaceutical, if patented;
3) declare that it cannot manufacture the pharmaceutical if the country is other than a least-developed country; and
4) indicate that the pharmaceutical is required to address a public health emergency if it is a country identified as being a more highly developed country (as set out in JCPA).

The Patent Act also identifies a specific list of pharmaceutical products that are eligible for export under JCPA. Currently, the list includes fifty-seven compounds including acyclovir, ceftazidime, ciprofloxacin, diphtheria vaccine, hepatitis B vaccine, ibuprofen, insulin injection, nelfinavir, and zidovudine. However, to remain effective in addressing the public health problems of developing and least-developed countries, the list may be amended to include additional compounds. Since its inception, the list of products eligible for manufacture and export under JCPA has been amended to include a fixed-dose combination of three antiretroviral drugs used in the treatment of HIV/AIDS.[4] The most recent addition to the list of products is Tamiflu (oseltamivir phosphate), a possible vaccine for avian flu.[5]

To obtain a compulsory licence under JCPA, a Canadian manufacturer must file a compulsory license application with the Canadian Patent Office.

The application must include

1) the name and quantity of the pharmaceutical product to be manufactured;
2) the country to which it is to be exported;
3) the identity of the patentee of the invention;
4) the name of the governmental person or entity who is purchasing the product; and
5) a declaration that the applicant had, at least thirty days prior to applying for the compulsory license, sought from the patentee(s) a license to manufacture and sell the pharmaceutical product.

Additional requirements may have to be satisfied to obtain a compulsory license, depending on the status of the importing country.

Assuming all requirements under the Patent Act are met, the minister of health must indicate that the product meets the requirements of the Food and Drug Act prior to the issuance of a JCPA compulsory license. In addition, products manufactured under JCPA must be distinguishable from the patented versions available in Canada, i.e., by specific markings, coloring, shape, and labeling. This is required to prevent re-importation of the licensed product into Canada or diversion to other countries not authorized to receive it.

Before export, the JCPA licensee must establish a Web site setting out detailed information regarding the licensed product, including name, distinguishing characteristics, amount to be exported, importing country, and all parties expected to come into contact with the product in transit to the importing country. The licensee must also, within fifteen days prior to export, provide a similar report to the patentee.

The amount of royalty payable by the Canadian compulsory licensee to the patentee is determined by multiplying the value of the purchaser agreement (the agreement with the importing country) with a royalty rate, which varies with the status of the importing country. Thus, the royalty rate is calculated on a sliding scale based on the standing of the importing country on the United Nations Human Development Index (UNHDI). Specifically, the formula for calculating the royalty rate is as follows: [(1 + no. of UNHDI countries – importing country's UNHDI rank)/no. of UNHDI countries] x 0.04.[6]

Where the importing country is not listed on UNHDI, the royalty rate is based on the average rank of all countries on UNHDI similar to the importing country. However, for unranked non-WTO developing countries that are not listed on the UNHDI, the royalty rate is based on the average rank of WTO member countries that have a similar level of development to the unranked non-WTO country.

Causes for Termination of a JCPA License

The court may terminate a JCPA license, upon application by the patentee, for due cause, including by reason of inaccurate information in the license; failure of the licensee to establish a Web site, provide an export notice, provide a copy of the supply agreement, or pay royalties; or diversion of the licensed product in defined circumstances, exportation of more product than authorized, and failure of the importing country to comply with certain obligations under JCPA.

JCPA also includes a clause, now referred to as the *good faith clause*, which provides the patentee with the right to challenge a license if there is cause to believe that the license is commercial in nature as opposed to humanitarian. As set out below, this is the case if the licensed pharmaceutical product is 25 percent or more of the average price of the patented innovative product in the Canadian market. The defense to such a challenge is proof that the product's price remains less than the manufacturer's supply cost plus 15 percent. A determination that the license is commercial in nature could result in termination of the license or payment to the patentee of an amount adequate to compensate the patentee for the commercial use.

Potential Limitations of JCPA

With the implementation of JCPA, Canada is the first WTO member country to implement the Doha Declaration and August 30, 2003, decision into its own legal system and practice. However, the question remains as to the extent to which this new compulsory licensing system will be utilized. Although JCPA has been in force for more than a year, there have been no license applications filed at the Canadian Patent Office as of the writing of this article.[7] Requirements of JCPA that may limit its utility to provide pharmaceuticals to developing and least-developed countries are outlined below.

Products for export under JCPA appear to require a regulatory approval process similar to that which applies to nongeneric pharmaceutical products marketed in Canada. This may limit its use; however, it is unclear as to the standards that Health Canada will apply to such products.

The term of the JCPA license is limited to a maximum of four years. This comprises an initial two-year term as well as a subsequent two-year renewal term where all product is not exported in the initial two-year term. Given the purpose of the legislation to address public health situations, some have claimed it would be more logical that the term be based on each given situation and the treatment period required to address the situation, rather than on what seems to be an arbitrary timetable.

The provision of a defined product list is another feature of JCPA that has been claimed to be contrary to its purpose of providing countries in need with access to pharmaceutical products, particularly if the pharmaceutical product required is not one that is on the list. Although it is possible that the list of eligible products may be amended, this process will inevitably take time, which may not be available in the case of a health crisis.

Potential Impact of JCPA on Research and Development

A country's system of patent protection does appear to impact the pharmaceutical industry's expenditure on research and development (R&D) as a whole. Indeed, a Canadian study by Bohumir Pazderak did find a correlation between increased patent protection with the implementation of bill C-22 in 1987 and increased pharmaceutical R&D spending.[8] Yet it is difficult, if not impossible, to conclusively demonstrate that any changes in R&D funding are due exclusively to the effects of a country's patent protection system.

Although no JCPA license applications have yet been filed, it is not known whether there will be any impact of this compulsory licensing regime on research dollars allotted within Canada. That being said, it is a fact that academic institutions play a critical role in the R&D activities of the pharmaceutical industry. For instance, a 1989 US survey of seventy-six US manufacturing companies found that 44 percent of the pharmaceutical industry's new products and 37 percent of its processes resulted from university research.[9] While these are US figures, it is fair to say that Canadian phar-

maceutical companies also view academic institutions as playing an important role in their development of new products. Furthermore, there are many incentives for pharmaceutical companies to invest research dollars into Canadian academic institutions including major tax credits and early access to innovative ideas and basic research. As such, it seems likely that the pharmaceutical industry will continue to provide funding to universities and other academic centers despite potential JCPA compulsory licenses under Canada's Patent Act.

Implementation of Similar Legislation in Other Countries

In addition to Canada, the European Union (EU), Norway, Switzerland, the Netherlands, Korea, China, and India are at various stages of implementing similar compulsory licensing legislation.[10]

A brief overview of the legislation implemented or being considered for implementation in these countries indicates that the legislation can vary substantially from country to country. The legislation implemented in both the EU and India appears to be quite relaxed in comparison to JCPA in Canada. For example, the EU permits companies to apply for a license to manufacture pharmaceutical products for export to countries in need without the authorization of the patent holder; however, there is no specific restriction on the products covered, although acknowledgement that the product to be exported is needed to address a public health problem is required.[11] The section of the Indian Patent Act dealing with the compulsory licensing of pharmaceutical products for export simply indicates that such licenses are available on application under the terms and conditions specified by the controller.[12] The *Manual of Patent Office Practice* published by the Indian Patent Office includes an editorial on these provisions indicating that they are to be construed in a wider sense to allow export to any country having insufficient or no manufacturing capacity in the pharmaceutical sector.[13]

On the other hand, the regulations proposed for the corresponding legislation in Norway is quite similar to JCPA. In Norway, although the pharmaceutical industry is relatively small and not many companies exist having the capacity to manufacture pharmaceutical products for export, the proposed regulations define a list of eligible countries, a list of applicable products, and a similar application process.[14]

Conclusion

Canada should be applauded for seeking to address the public health needs of developing and least-developed countries through the implementation of JCPA. JCPA represents initiative by the Canadian government to exhibit social responsibility and has provided a basis for other countries/regions to follow suit including the EU, Norway, Switzerland, China, and Korea.

JCPA provides a means by which low-cost pharmaceuticals can be supplied to countries in need. However, in the process of trying to provide a compulsory licensing regime that yields the appropriate balance of rights between the pharmaceutical research-based and generic-based sectors, JCPA includes requirements excluded from previous compulsory licensing regimes in Canada that may impede this purpose. For example, the two-year term of a JCPA license (with an ability to extend for another two-year period in certain circumstances) appears contrary to the purpose of the legislation to provide the developing world with access to needed pharmaceutical products. In addition, JCPA compulsory licensing can be used for a defined list of products that has been argued to be inconsistent with the aim of providing access to pharmaceutical products in the event of a public health crisis, although additions to this list are possible and have already been made.

While theoretically the new amendments to the Patent Act alter Canada's patent regime, it seems unlikely that the new compulsory licensing system will result in any drastic changes on the part of the pharmaceutical research-based sector in Canada, for example, in R&D activities.

Indeed, the commissioner of patents in Canada has yet, as at the time of writing, to receive a compulsory license application under JCPA, despite the continued existence of health crises in the developing world. This should not be viewed in a negative light, however, given the nature of pharmaceutical manufacturing and the ramp-up times required. Given that both a combination treatment for HIV/AIDS and a vaccine for avian flu have recently been added to the JCPA product list, it is possible that a JCPA license application is on the horizon.

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Surveying the Need for Technology Management for Global Health Training Programs

Usha R. Balakrishnan, MBA, Lisa Troyer, PhD, and Edwin Brands, PhD

Abstract

Technology licensing office managers often need to evaluate profitability and commercial potential in their decision making; however, increased consideration of important global public health goals require forging new collaborative relationships, incorporating creative licensing practices, and embracing global public good within academic and research communities. The authors conducted a survey to identify and document opportunities and barriers to the management of discoveries and inventions arising from global health research outcomes at US and Canadian academic and research institutions.

Introduction and Background

Technology licensing office (TLO) managers typically perform a multitude of tasks, from evaluating inventions for marketability; to educating researchers on key intellectual property issues; to crafting licenses that are mutually beneficial to researchers, the university, and private industry. In the past several years, global health (GH) technology transfer is emerging as an internationally significant field, both in terms of research and technology management.[1] As in many other fields, research institutions play a vital role in the development and clinical testing of new cures for diseases by conducting basic research and forming partnerships to transfer findings to the marketplace.[2] Yet, vaccines, drugs, and diagnostics for devastating diseases such as AIDS, malaria, tuberculosis, and a whole host of so-called neglected diseases are inadequate or nonexistent because there is little economic incentive for the private sector to develop new drugs.

Usha R. Balakrishnan, MBA, is founder of the AUTM Special Interest Group, Technology Managers for Global Health, and founding president and chair of the board of CARTHA, a global nonprofit organization based in Iowa City, Iowa. Lisa Troyer, PhD, is professor of sociology and administrative fellow in the Office of the Provost and Edwin Brands, PhD, is adjunct assistant professor of geography at the University of Iowa in Iowa City.

To address the formidable challenge of developing health products for neglected diseases, several global public-private product development partnerships (PDPs) have been formed and supported by philanthropic organizations as well as national governments.[3, 4, 5] These nonprofit global PDPs remove or reduce some of the risk associated with developing drugs for markets in which there is (or is perceived to be) a limited payer market, thus motivating firms to invest capital and making drug development for neglected diseases possible.[6] Increased TLO manager consideration of the potential contributions of new health research and development (R&D) and product innovations to address important global public health goals (i.e., reduction of disease burdens among millions of affected poorer populations in developing countries) will require forging new collaborative relationships, incorporating creative licensing practices, and embracing global public good within academic and research communities.

The TLO's primary mission is to ensure that publicly funded research is translated into products for the benefit of the public.[7] From the managerial viewpoint, this primary mission guides operational strategy development. Technology licensing office managers routinely interact with researchers from a variety of scientific disciplines as well as executives from diverse industrial sectors. In this sense, TLO managers serve as *cultural translators*, or bridges between several professions, academic disciplines, industry, and technology sectors. Technology licensing office managers can be likened to artisans[8] in that they develop real-time specialized and customized approaches to managing inventions, inventors, licensees, and the entire negotiation process involved in complex deal making. Technology licensing office managers, in their gatekeeping role, can thus address the significant challenge of opening new channels and forming networks for the development of innovations that address both economic and social good.[9,10,11,12]

Significant costs involved in intellectual property (IP) rights protection often constrain TLO managers' patent-filing decisions to two criteria: patentability and commercial potential, including an assessment of whether a third-party sponsor or licensee is willing to reimburse patent-prosecution expenses. The nature of the academic patent-licensing environment requires balancing profitability with public benefit, as commitments of $15,000 or more are made per patent filing. Financial commitments of this nature cre-

ate pressure both within TLO operations and from university administration for TLOs to generate substantial funds for the institution to (a) justify sustained investments in TLO staffing and operational budgets; (b) enhance prospects for additional revenue-producing patent portfolios under TLO management; and/or (c) contribute to economic growth via technology-based entrepreneurial startup companies, new job creation, or new business recruitment in a local/regional setting.

Patent-filing decisions and subsequent licensing tactics and negotiation strategies employed by TLO managers significantly impact sequential trajectories and development pathways involved in translating nascent university-based discoveries into products that benefit society. Technology licensing office managers thus are key gatekeepers; their managerial role in facilitating timely interactions within the continuum of scientific R&D, discovery, and product development is critical.

Facilitating the training of TLO managers who want to actively consider the GH implications of their work is an essential step in enabling individuals and institutions to launch forays in this area. This type of training may lead to uniquely refined roles for TLO managers and their institutions in promoting GH partnerships. Much as technology transfer activity has evolved over the last three decades, such new training and ensuing dialogs may help formulate new approaches and models that universities can utilize to catalyze partnerships in the GH arena. Enabling effective pursuit of the TLO's public benefit mission has the potential to extend the impact of TLO managers' (and their institutions') work into broader global contexts. New informational resources and training curricula have been designed and developed under collaborative efforts between AUTM and its Better World Project; AUTM's Special Interest Group, Technology Managers for Global Health; and MIHR-Centre for the Management of IP in Health R&D.[13,14,15,16]

Indeed, the AUTM 2006 Annual Meeting℠ was dedicated to the theme of "Improving Society," with an emphasis on GH technology transfer.

Survey of US TLO Managers

The purpose of our survey is to systematically identify and document barriers to the management of discoveries and inventions arising from GH research outcomes confronted by TLO managers. (The University of Iowa's Institutional Review Board approved the protocol and instrument for our

survey [IRB #200503752]). Discoveries and inventions arising from GH research may not fit the profile of conventional types of innovations with which TLO managers are familiar. Our survey assesses this concern to gain a more complete understanding of how the unique profile of innovations from GH research fits (or does not fit) within the structure of existing technology licensing decision making and procedures. This understanding could inform the development of new resources and infrastructure that may be needed to support the ongoing and future work of TLO managers in GH.

The two-part questionnaire contained thirteen questions: Part I requested descriptive information (e.g., external research dollars, age of the TLO, number of invention disclosures) regarding TLOs and institutions. Part II was aimed at specific activities pertaining to decision making and barriers to, experience with, and interest in promotion of GH discoveries in TLOs. To avoid conflict of interest for the first author (Balakrishnan), only the second author (Troyer) was involved in data collection and analysis and only the second author has access to the data.

Sampling and Response Rate

The AUTM membership's institutional affiliations comprised our sampling frame. One questionnaire was sent via postal mail to the director of each US or Canadian TLO. Instructions indicated that respondents should reply anonymously. We mailed 385 questionnaires; 240 were returned for an initial response rate of 62.34 percent. Of these, 24 did not answer any of the survey questions, leaving an analyzable response rate of 56.10 percent (n = 216).

Descriptive Profile of TLOs

Table 1 reports the characteristics of the TLOs in our sample. A comparison of means and medians reveals that the sample is somewhat skewed, with a few very large offices driving up mean values. Only 40 respondents out of 198 (20.2 percent) reported licensing income above $4 million; respondents to our survey primarily represented relatively small offices. Approximately half of the offices in our sample have been in existence for eleven or fewer years. The median office is relatively small with two professional and one support staff, processing thirty-four disclosures and executing six patent licenses/options, with a licensing income of $700,000 and external research dollars between $20 and $99 million, annually.

Table 1:
Means, Standard Deviations, and Medians for Characteristics of Technology Licensing Offices in the Sample

Characteristic	Mean (SD)	Median
Age of TLO (in years) (n = 210)	14.68 (11.79)	11
Number of professional staff (n = 213)	3.46 (5.49)	2.0
Number of support staff (n = 213)	2.54 (4.17)	1.0
Number of invention disclosures in 2004 (n = 207)	79.82 (120.89)	34
Number of patent licenses/options executed in 2004 (n = 204)	20.33 (35.73)	6
2004 licensing income (in millions) (n = 198)	4.38 (1.15)	0.70
External research dollars received (in millions) (n = 213)	N/A	$20 – $99

The majority of respondents (62.5 percent) report to a research office. The second most common reporting line was to either an academic affairs office (including provost) or president (12.5 percent each). The next most common reporting line was to a foundation office (9.2 percent). Only 4.6 percent indicated reporting lines to corporate affairs, public affairs, or other offices.

Factors Affecting Evaluation of Patents/Disclosures and Attention to Global Public Health Technologies

To identify opportunities for advancing technologies related to global public health, we must first understand TLO decision-making processes in general. We asked respondents to report on the relative importance of eight criteria that might affect technology evaluation. Responses (Table 2) were indicated on a scale from 1 (not at all important) to 7 (extremely important), with the scale midpoint of 4 (somewhat important).

Table 2:
Means and Standard Deviations for Importance of Criteria in Patent/Disclosure Evaluations

Criterion	Mean (SD)
Patentability (n = 216)	5.94 (0.97)
Availability of budgetary resources for patenting (n = 216)	4.48 (1.80)
Anticipated availability of third-party reimburser for patent costs (n = 216)	4.63 (1.72)
Immediate commercialization prospects [n = 216]	4.75 (1.41)
Long-term commercialization prospects (n = 216)	5.86 (1.20)
Research funding prospects (n = 216)	4.06 (1.65)
Potential for forming startups to aid local economic development (n = 216)	4.12 (1.61)
Ability to promote development of inventions and technologies that address treatments for diseases of poverty (n = 189)*	3.46 (1.80)
Other (n = 27)**	5.44 (1.87)

*This item was elaborated for respondents in the survey as "so-called 'neglected diseases' such as AIDS, tuberculosis, malaria, Chagas, leishmaniasis, African trypanosomiasis, dengue fever."
**Respondents were permitted to suggest criteria other than the eight that we listed and to provide a rating of the importance of each criterion that they suggested. Other criteria mentioned included interest of researchers, interest of administrators, and institutional strategic initiatives.

Patentability (mean = 5.94) and long-term commercialization (mean = 5.86) were rated highest in terms of importance, with "other" criteria (mean = 5.44) related to interests of administrators and researchers, as well as the strategic initiatives of the institution. Technology related to treatments for diseases of poverty was rated least important (mean = 3.46, somewhat important). On average, all of the criteria except "technologies related to treatments for 'diseases of poverty'" were more than somewhat important. The results are suggestive of the dominant importance of financial drivers and direct economic implications in evaluations related to patents/disclosures.

From a programmatic standpoint, these results suggest the importance of making the economic implications of attention to technology related to treatments for neglected diseases salient. That is, to facilitate the embrace of the global public good on the part of academic and research communities, there must be a broader understanding of and appreciation for the economic impact that attention to neglected diseases has the potential to impart.

Next, we asked respondents to rate the extent to which different factors obstructed the pursuit of technology transfer related to global public health within their offices. Responses (Table 3) for these factors ranged from 1 (not at all an obstacle) to 7 (substantial obstacle), with a scale midpoint of 4 (somewhat of an obstacle).

Table 3:
Means and Standard Deviations for Extent to which Factors Are an Obstacle in the Pursuit of Technology Transfer Related to Global Public Health

Factor	**Mean (SD)**
Lack of faculty research/interest (n = 189)	4.08 (2.06)
Lack of reasonable flow of GH-related invention disclosures (n = 189)	5.49 (1.39)
Lack of expertise within office in area of global public health inventions (n = 189)	3.24 (1.79)
Lack of revenue-generating potential from global public health inventions (n = 183)	3.64 (2.08)
Lack of external funding available for global public health research (n = 168)	4.38 (2.06)
Lack of relationships with professional organizations or networks with goals of advancing global public health partnerships (n = 177)	4.15 (1.78)
Lack of support from senior administration (n = 180)	2.68 (1.93)
Lack of time to allocate to projects with less income-generating potential (n = 183)	3.92 (1.96)
Other (n = 6)*	6.00 (1.10)

* Respondents were permitted to suggest criteria other than the eight that we listed and to provide a rating of the extent to each criterion that they suggested was an obstacle. Other factors included not a strategic priority, not enough personnel, and lack of awareness of what inventions are related to global public health.

It may seem paradoxical at first that "lack of time to allocate to projects with less income-generating potential" and "lack of revenue-generating potential from global public health inventions" are viewed as less than somewhat of an obstacle, on average, in the pursuit of global public health technologies (respectively, mean = 3.92 and mean = 3.64). Yet, these survey items reflect a fine distinction from those in Table 2. Items in Table 2 reflect general factors that influence evaluations of patents/disclosures,

whereas the items in Table 3 reflect particular barriers to global public health technology transfer. These findings may indicate that, while positive financial and economic effects are important in the general evaluation of patents, TLO directors recognize that other factors may govern inventions and discoveries related to technology transfer within global public health (and perhaps other) domains.

For instance, Table 2 suggests that "*ability* to promote development of inventions and technologies that address treatments for 'diseases of poverty'" (emphasis added) is the least important of the factors listed in the table that contribute to evaluations of patents/disclosures (mean = 3.46). That is, the TLO's competence is not perceived as an issue. What is? Table 3 reveals that there may be a problem with the pipeline of discoveries: "lack of reasonable flow of global health-related invention disclosures" shows the second-highest highest mean value (5.49) as an obstacle to technology transfer related to GH. On a related point, note that "lack of support from senior administration" is, on average, viewed as less than somewhat of an obstacle (mean = 2.68). This further supports the notion that institutions may not be entirely driven by financial and economic concerns in the arena of technology licensing activities. Moreover, it again suggests that education may be a strategy for enhancing technology transfer as it relates to global public health.

Aside from the "other" factors, the factor viewed, on average, as the greatest obstacle was "lack of GH-related invention disclosures" (mean = 5.49), followed by "lack of external funding for GH-related research" (mean = 4.38). We suspect that these two factors are interrelated: the lack of funding likely affects research, which drives inventions (and subsequently disclosures). This suggests two programmatic directions. First, institutions seeking to increase technology transfer related to global public health must help researchers identify external funding. Second, they must develop strategies to advocate for attention to GH on the part of external funding agencies and foundations.

This latter direction reiterates a common theme in our research: the need to educate researchers, funding agents, and the public regarding the potential positive economic and social impacts of attention to global public health. The former direction (i.e., identify funding opportunities) might also address other factors that are greater obstacles, such as faculty interest.

Identification of funding opportunities may pique faculty interest in pursuing research that leads to technologies and inventions that address global public health issues, although note that lack of interest is just barely above the scale midpoint, corresponding to somewhat of an obstacle. Yet, this does not suggest that we can ignore the fact that faculty research is a key driver of licensing activities. Consequently, raising faculty interest in and research related to GH innovations remains important to addressing GH needs.

Table 3 also foreshadows a potentially important strategy for moving in these directions. Note that "lack of relationships with professional organizations or networks with goals of advancing global public health partnerships" is, on average, slightly more than somewhat of an obstacle (mean = 4.15). We are able to further explore this finding through the results presented in Table 4, which provides the number of respondents reporting that their TLO was engaged in specified partnerships within the last year.

Table 4:
Frequency of Technology Licensing Office Partnerships Related to Global Public Health

Partnership	**Frequency**
International AIDS Vaccine Initiative (n = 213)	15
Medicines for Malaria Venture (n = 210)	12
Malaria Vaccine Initiative/PATH (n = 213)	15
Global Alliance for Tuberculosis Drug Development (n = 213)	21
Aeras Global Tuberculosis Vaccine Foundation (n = 210)	0
International Partnership for Microbicides (n = 213)	n < 5
Pediatric Dengue Vaccine Initiative (n = 213)	n < 5
Foundations for Innovative New Diagnostics (n = 213)	6
Institute for One World Health (n = 216)	15
Drugs for Neglected Diseases Initiative (n = 213)	0
Other (n = 16)*	18

*Other partnerships mentioned were Medicine in Need, Global Vaccines Inc., Public Intellectual Property Resource in Agriculture, Foundation for Innovative New Diagnostics, Grand Challenges in Global Health, Global AIDS Vaccine Initiative, Doctors Without Borders, Rotary International, and Private Corp. for HIV Vaccine.

Perhaps the most compelling result suggested by Table 4 is the dearth of partnerships. Overall, there was very little reported activity involving these GH-related public-private partnerships. The Global Alliance for Tuberculosis Drug Development showed the most activity (respondents from twenty-one offices). Yet this represents less than 10 percent of the sample. In the Summer 2004 edition of the *Journal of the Association of University Technology Managers*, Charles Gardner and Cathy Garner note the potential of such partnerships, but also acknowledge their newness.[17] Thus, programmatic attention might be given to facilitating ties between TLO managers and staff with such partners and networks. Proactive site visits to institutions, joint conferences, and the development and dissemination of curricular training materials that include lists of such organizations may catalyze more research in this arena.

Education and Training Related to Global Public Health Technology Transfer

The above analyses provide a strong indication of the potential of training and education for impacting the level of activity related to global public health technology transfer. Our survey also probed TLO directors in this regard. One hundred and ninety-two of 216 respondents (88.9 percent) reported conducting educational seminars. This suggests the recognition that ongoing training is critical to the rapidly evolving field of technology transfer. Only 9 (4.7 percent) of 192 respondents reporting the presence of educational seminars at their institutions incorporated a GH component in their seminars. While on the face this may seem discouraging, we view it as an important opportunity. To further exploit the emergence of this opportunity, we asked respondents to report on the value of different elements that might comprise training and educational seminars related to global public health. Respondents were asked to rate the usefulness of elements of curricula to enhance global public health management activities. Responses were made on a scale from 1 (not at all useful) to 7 (extremely useful), with a scale midpoint of 4 (somewhat useful). Table 5 summarizes these results.

Table 5:
Means and Standard Deviations for Usefulness of Educational Curricula Elements Involving Global Public Health Management Activities

Curriculum Element	**Mean (SD)**
Case studies (n = 180)	4.78 (1.56)
Sample licensing language (n = 192)	5.05 (1.79)
Standard humanitarian purpose licensing provisions (n = 186)	5.03 (1.72)
List of potential GH partners (n = 183)	5.52 (1.50)
List of funding opportunities (n = 189)	5.75 (1.69)
Directory of experts/technology managers experienced in GH technology management (n = 189)	4.71 (1.59)
Other (n = 15)*	5.80 (2.48)

* Respondents were permitted to suggest elements other than the six that we listed and to provide a rating of the extent to which the elements that they suggested would be useful. In nearly every case in which a designation was made under "other," however, the elements listed were not given or were redundant with the categories above. Consequently, this result is not interpretable.

Perhaps the most striking feature of Table 5 is that all of the six elements were rated as more than somewhat useful. Aside from the "other" category, the most useful criteria, on average, appear to be "list of funding opportunities" and "list of potential GH partners" (respectively, mean = 5.75 and mean = 5.52). This highlights the importance of knowing who and where when it comes to supporting technology licensing activities. To the extent that global public health technology transfer activities may be emergent among the academic and research institutes we surveyed, the need for this information may be particularly keen.

The results in Table 5 also suggest the potential value of providing template processes, language, and provisions related to licensing global public health technologies. Respondents indicated that sample licensing language, standard humanitarian purpose licensing provisions, and case studies would all be more than somewhat useful in the development of education and training seminars related to global public health management activities (respective means = 5.05, 5.03, 4.78).

Finally, the importance of human resources is indicated in Table 5. Respondents indicated that a directory of experts/technology managers experienced in GH technology management would be useful in developing curricula (mean = 4.71). Until activities surrounding global public health technology management become more common, experts may not be highly visible. Consequently, targeted efforts to identify them and encourage others to seek their expertise may facilitate advances in global public health technology management.

Study Limitations

Although the response rate (56.10 percent) falls within the rule of thumb for adequate with respect to surveys of this nature (i.e., anonymous, sent via postal mail),[18] we must consider the biases that may be reflected in a less-than-100 percent response rate. In this case, it was clear from our cover materials and the questionnaire itself that our interest was in examining technology transfer as it relates to global public health. Nonrespondents may be less interested, experienced, or supported in this area. Consequently, we might conservatively limit our interpretation of these results to groups with at least a minimal interest in and institutional support for the pursuit of global public health technology transfer.

Second, it is important to recognize the profile of the institutions whose representatives participated in our study, most of which are relatively small institutions in terms of both staff size and activity level. These may be precisely the kinds of institutions at which resources (especially information and human resources) are particularly scarce, making advances in an emergent area, such as global public health technology management, very challenging.

Third, on a related point, our survey represents a snapshot in time regarding a limited set of factors affecting global public health technology management activities. Longitudinal trends could not be discerned from our survey. Moreover, there may be other variables that we did not systematically explore that affect these activities (e.g., local, regional, and global economic conditions; advances in complementary technologies; local, regional, and global events).

Fourth, in an attempt to ensure that the items on our instrument were exhaustive, we liberally included an "other" response category and encour-

aged respondents to provide their own insights on the questions we asked in case our response categories did not accurately capture a respondent's view/experience. This response category was generally used by less than 10 percent of the respondents (the exception being responses to our query regarding the importance of criteria in patent/disclosure evaluations [for "other," $n = 27$]), suggesting that, for the majority of our respondents, the categories effectively captured their views/experiences. Nonetheless, the survey could be improved by adjusting the response categories to subsume the points respondents raised in "other" responses. Furthermore, and related, the survey may be improved by validating items and reliability assessments. Of course, this requires repeated administrations of the survey, as well as considerations regarding its length (generally reliability and validity are best assessed by incorporating multiple items designed to tap the same construct). Thus, balancing the survey length (which can have a profound effect on response rates) with considerations of validation and reliability assessment would be an important consideration in any future administrations of it.

Discussion and Conclusion

Despite some limitations, the results of our research shed new understanding on processes surrounding global public health technology management activities. First, although financial and economic considerations are critical in licensing activities, this does not close the door to the pursuit of global public health technology transfer. Likewise, the role that faculty research plays in catalyzing licensing activities must be recognized and addressed. Finally, the resources and support available to TLOs—within their own institutions and new resources from external sources—may be avenues that need to be addressed in spurring activities related to global public health.

Toward these ends, our study suggests the importance of educating technology licensing professionals, researchers, and institutions regarding the economic impact of global public health technologies. A key element of such education is likely a broad (both geographically and temporally) view for recognizing and embracing global public view from social, economic, and humanitarian standpoints. The field for such education may be particularly fertile, insofar as our survey results suggested that TLOs do not (on average) experience resistance from senior administrators when it comes to global public health technology management activities. Still, further investigations related

to the content of such a curriculum and the optimal method of delivery is needed.

Second, our research suggests specific avenues that may be taken to enhance global public health TLO activities. Specifically, our investigation suggested that there might be a promising opportunity to educate TLOs regarding the process through which global health technologies are effectively managed.

Third, the results of our survey suggest that human resources may be a particularly important resource. Brokering professional relationships between those with and those without experience in global health technology management activities appears to be vital to enhancing these activities.

A recent survey of industry licensing executives indicated that personal connections between inventors and industry R&D staff were the most important source of university technologies, accounting for more than half of licenses.[19] However, as bridges between professions, academic disciplines, industry, and technology sectors, TLO managers are uniquely positioned to influence technology transfer. Because GH technology transfer does not operate through existing university-industry channels, TLO managers' bridging role may become even more important. Yet establishing and/or strengthening such bridging roles requires key resources, including access to professional networks, legitimacy within one's own institution, and information and knowledge. Such resources are not always easy to secure and are often very difficult to disseminate to others, particularly when they involve an emerging area of activity, such as global public health technology management. Moreover, given the extreme budgetary pressures within many TLOs, the tangible costs to support a TLO managers' interest in GH technology transfer may not be forthcoming or readily available from their institutions (unless those TLOs or institutions already have home-run patents that offer the financial flexibility to support new activities including release time, professional development activities, travel, outreach, and IT infrastructure support). Thus far, no systematic effort has been undertaken to identify practical strategies, adequate resources, and supportive internal and external infrastructure to capitalize on new opportunities and foster the involvement and training of a generation of leaders in technology transfer, particularly in fields related to GH. We believe that our early work, aimed at enhancing collective good, offers a timely and important contribution in this direction.

Acknowledgements: This work was supported through funding from the Rockefeller Foundation (Grant HE 039) to the University of Iowa and the Ewing Marion Kauffman Foundation (Grant #20060613) to MIHR - USA. The contents of this publication are solely the responsibility of the authors. We are grateful to the anonymous respondents who participated in the survey supported by this grant. Additionally, we appreciate the insightful and constructive comments of Paul Greenough and Lavanya Murali on the questionnaire and other elements of this project. Ashley Stevens, Sandy Shotwell, Lita Nelsen, and Nalini Anand provided helpful feedback on earlier drafts of the survey instrument. We thank them for their useful comments. Finally, we are grateful to the ten anonymous reviewers for their constructive comments on earlier drafts, which facilitated substantial improvements to the manuscript.

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Legalink: Why Provisionals Need Claims

Todd L. Juneau, JD

Abstract

Obtaining patent protection for a university invention can be a costly and time-intensive proposition, so many universities file provisional patent applications. But provisionals should not be considered "quickie" patent applications as the resulting application probably will neither satisfy potential licensing partners nor provide a sufficient platform on which to build a patent portfolio. Regardless of whether the US Patent and Trademark Office *can or will* accept a provisional application as a valid filing, even without any claims or sequence listings, there are still other patentability requirements, namely the written description requirement and the enablement requirement, that must be met for a regular patent application, filed at around the one-year date, to claim priority to the provisional filing date.

Introduction

Most veterans of technology transfer are fairly well-acquainted with the benefits of using provisional applications. The filing fee is much less, you defer examination by a year, and there is less paperwork since declarations and assignments don't have to be filed. Some even know that it's a good idea for non-US companies and universities to file a US provisional because foreign references are only effective as of their US filing date under 102(e), and this is a great way to stay ahead of the competition. However, there is a worrisome line of thinking that provisionals can also be "quickie" patent applications, where all you do is slap a cover sheet on a professor's draft manuscript, and voilá, you have a filing date.

But what about including claims? sequence listings? deposits of microorganisms?

Todd L. Juneau, JD, is a patent lawyer and the managing partner of Juneau Partners PLLC in Alexandria, Virginia.

Unfortunately, the answers to the above questions are (1) definitely, yes; (2) probably a good idea; and (3) ditto—a good idea. This is unfortunate because it puts all of those quickie applications on the risk-management track instead of the licensing track.

If you're short on time, but still want to know the reason why provisional applications should include claims and, in the case of biotechnology applications, sequences, here it is: Regardless of whether the US Patent and Trademark Office *can or will* accept a provisional application as a valid filing, even without any claims or sequence listings, there are still other patentability requirements, namely the written description requirement and the enablement requirement, that must be met for a regular patent application, filed at around the one-year date, to claim priority to the provisional filing date. And, without the earlier date, any publication of the invention can be a bar to patentability.

Claiming Priority

Claiming priority is governed by 35 USC 119(e), which allows a provisional and subsequent application for examination to link to one another such that the regular patent application can adopt the earlier filing date of the provisional. In other words, applicants who file a provisional can maintain their original filing date when they resubmit the application to enter the examination process. Without a claim to the earlier date, patent rights would be jeopardized by papers and abstracts being published, posters being presented, or third-party patents being granted.

There are only four requirements to be able to claim this earlier date: (i) there must be at least one common inventor between the two applications, (ii) there must be some common inventive disclosure in the two applications, (iii) the two applications must overlap in time, i.e., be copending, and (iv) the applicant or his or her attorney must amend the regular application to reference the earlier one. It helps to remember these requirements by thinking of them as The Four Cs: common inventor, common invention, copendency, and contains reference to the earlier filing.

Provisional Requirements

Provisional patent applications are governed by another law, 35 USC 111(b). This is in contrast to section 111(a), which governs regular patent

applications, also known as examination patent applications.

Section 111(b)(1) requires that a provisional application *shall* include (1) *a specification as prescribed by the first paragraph of section 112* (emphasis added) of the patent laws and (2) drawings as necessary. Section 111(b)(2) also specifically says that a claim shall not be required in a provisional application. Thus, it is optional, right? Maybe, but I don't recommend taking the bait.

Enablement and Written Description

All patent applications—provisional and regular—must comply with the enablement and written description requirements, namely the first paragraph of section 112 of the patent laws.

Enablement, in short, is a term of art used to describe when a patent specification contains "full, clear, concise, and exact" enough directions that any person skilled in the art to which it pertains can make and use the invention. I like to think of it as a box of parts with the step-by-step instructions for connecting each part to the next along with a description of how to use the final product.

The written description requirement of the first paragraph of section 112 is more of a comparison of the final product to how the patent claims are worded. The patent laws, regulations, and court decisions have had an awful lot to say about this requirement, but suffice it to say that the test has been one of possession and completion. If an applicant has actually made a working prototype and has described in words, structures, figures, diagrams, or formulas how a person of skill will know that the invention, as claimed, was put together correctly, the requirement is satisfied. In other words, written description concerns the distinguishing and identifying characteristics of the final product, or as I think of it, how do you know that you have built what is claimed?

But how can a provisional without claims lead to an invalid patent and what does the written description requirement have to do with anything?

The short answer is that there is an inconsistency between the US Patent and Trademark Office (USPTO) "allowing" applicants to file without claims or sequences and the priority requirements that have an underlying requirement to have claims to satisfy the written description and sequences to satisfy enablement.

The USPTO Position

To support this proposition, I offer the USPTO's own rules on this matter. The USPTO publishes rules concerning patentability and patent examination procedures in a volume called the *Manual of Patent Examination Procedure* (MPEP).The MPEP is the USPTO's official publication on the patent laws and rules and also is its opinion on various unsettled points of law. It is, to the USPTO's credit, a fairly accurate description of "the law" subject to a few exceptions.

The MPEP has twenty-seven chapters, seven appendices, and is regularly updated to reflect changes in case law. In particular, MPEP 608.01(k) discusses when a patent application is complete (or incomplete) and states that "the claims define the invention." Taken the other way around, without claims, an invention is undefined. But here's the rub—if a provisional has no claims and the invention is, therefore, "undefined," then how can the same application also be said to be "fully, clearly, concisely, and exactly" described as required under section 112, first paragraph? The answer is that it probably can't. It's like a box of parts with no drawing of what it should look like once the parts are connected. Therefore, the application wouldn't satisfy the first paragraph of section 112 and, further, would not be entitled to support a claim of priority for a regular application that was relying on it for a filing date approximately one year earlier. Oops. Companies' fortunes and entire patent portfolios have been lost by being one day short in the race to get a patent application on file. Imagine what picking up your filing date flag and moving it forward an entire year along the timeline can do to patent rights?

Facts of Life: Raising the Bar

In this regard, one fact of life in the patent/research world is that you're never alone: there are a lot of very intelligent people trying to find solutions to the same problem at the same time. Given that it is a near certainty that there are other inventors working in the same field, there will probably be one or more publications that come out during that one-year provisional period, maybe even your own publications, that can be expected to act as a publication bar once your filing date moves forward one year.

Another section of the MPEP, MPEP 2163.03, states it even more forcefully and recites several famous federal cases to the effect that "to satisfy the

written description requirement, a patent specification must describe the *claimed* invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the *claimed* invention." Further, "compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention *claimed*" (emphasis added).

Now, you might be asking yourself, why would the USPTO mislead applicants and allow them to file provisionals without claims? Good question. The following case is illustrative.

Written Description and Provisionals: New Railhead Manufacturing

New Railhead Manufacturing LLC owns US Patent Nos. 5,899,283 and 5,950,743, drawn to a drill bit for horizontal directional drilling of rock formations and a method for horizontal directional drilling. New Railhead sued Vermeer Manufacturing Co. and Earth Tool Co. for infringement in the US District Court for the Northern District of Texas because VerMeer and Earth Tool were manufacturing and distributing a competing drill bit. However, both patents were invalidated at trial. New Railhead appealed to the Federal Circuit Court of Appeals and, in a decision in July 2002, lost when the appeals court affirmed that the lack of priority invalidated the patents.

Why were the patents invalidated? Because the patents lost their claim to priority by failing to satisfy written description in the underlying provisional.

The patents in suit were filed as continuation-in-part applications that claimed the priority date of a provisional application filed by New Railhead on February 5, 1997.

The Court of Appeals correctly stated the law, namely for the nonprovisional utility application to be afforded the priority date of the provisional application, the two applications must share at least one common inventor and the written description of the provisional must adequately support the claims of the nonprovisional application.

But what does that *mean*? It means that, for a patent specification to properly support claims, it has to be drafted using the exact same words in the body of the application that you plan to use in claims. For example, imagine trying to convince the examiner to let you overcome a piece of prior art by just inserting a new word into the claims that has never been used in the patent application. He might ask you, where did you get that word?

And, when you fail to point to a specific line and paragraph in the patent application, he will properly deny your amendment. Applicants are not allowed to use words in their claims that are not found in the body of the application.

Now, imagine this scenario: you've developed a fine new drill bit and your patent lawyer has done a good job describing it in a patent application. He has added all the new features of the commercial product into the later filed examination application. Unfortunately, the exact language to describe these features was not worked out a year earlier before the provisional was filed, but most of the concepts were there and, anyway, claims were not "required" in the provisional, right? The result: the patent that eventually grants will be invalid because the exact language used in the granted claims, although successfully written into the later examination application, were not included in the earlier provisional, so the claim to priority will fail; just like New Railhead.

It is important to note that it is the applicant's job to look out for himself because the patent examiners merely enter a priority claim as a procedural act, and they do not check your earlier filing to see if it actually supports your later filed claims.

Enablement and Provisionals: Invalidity from Missing Sequences in the Priority Document

In *Fiers v. Sugamo*, 25 USPQ2d 1601 (Fed. Cir. 1993), the Court of Appeals for the Federal Circuit stated as follows: "An adequate description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it; what is required is a description of the DNA itself."

In *Fiers*, priority was denied to a claim because the DNA sequence coding for a specified protein was absent in the priority documents. When was the last time you heard of a university filing a sequence listing along with its provisional application?

And this is not an isolated case. In *Fiddes v. Baird*, 30 USPQ2d 1481 (Bd. of Appeals 1993), a similar decision occurred where the board of appeals stated that "knowledge of amino acid sequence of a protein coupled with the established relationship in the genetic code between a nucleic acid and a protein it encodes would not establish possession of a gene encoding that protein." In other words, priority was lost because the DNA sequence was not submitted

even though the complementary amino acid sequence was available.

Enablement and Provisionals: Ex parte Forman

In *Ex parte Forman*, 230 USPQ 546 (Bd. of Appeals 1986), the board of appeals at the USPTO considered a claim a class of oral vaccines made from genetically engineered hybrid bacteria. To produce the hybrid, the inventors used a process that involved using mutant strain of typhoid *Salmonella* (*S.typhi*).

In biotechnology applications, where a patent application involves an organism, the applicants are required to provide a frozen sample of the organism to an approved facility, e.g., the American Tissue Culture Collection (ATCC), as a way to "enable a person in the field to make and use the invention." Although, the final hybrid bacteria was deposited with the ATTC, the mutant strain used in the intermediate process was not.

The patent examiner rejected the claims because the *S. typhi* had not been deposited and, thus, the application was not enabled. The board of appeals upheld the examiner, since without the deposit of mutants of *S.typhi*, the invention could not be replicated by a person in this field. A tough result, given that the applicant had, in fact, provided a deposit commensurate with the final product, just not the process of getting there.

Now imagine trying to maintain a provisional filing date as a priority claim. When was the last time you have heard of a university making an ATCC deposit under the Budapest Treaty as part of the provisional filing? To be fair, this exact issue has not been litigated and become standard case law. However, *Ex parte Forman*, although it was only a case solely within the USPTO legal system, it was cited with approval by the Court of Appeals in another major enablement case, see e.g., *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Final Thoughts

Just because the USPTO will accept a provisional without claims doesn't mean that it's a good idea. Relying on the good will of a federal judge in a later patent proceeding to determine what you invented in the absence of any claims to guide him or her to save your provisional filing date also doesn't seem like a good idea.

Portions of this article were previously published on the Internet.

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Contact Information

Association of University Technology Managers
60 Revere Dr., Suite 500
Northbrook, IL 60062
Phone: 847/559-0846
Fax: 847/480-9282
E-mail: info@autm.net
Web site: http://www.autm.net