

PENN'S INNOVATIONS AND THE GLOBAL POOR
FACILITATING ACCESS TO MEDICINES IN DEVELOPING COUNTRIES

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Universities Allied for Essential Medicines

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● EXECUTIVE SUMMARY ○

According to the World Health Organization, one-third of the world's population lacks access to needed medicines. Millions more suffer from neglected diseases, those that predominantly afflict people too poor to constitute a market attractive to private-sector R&D investment. This working paper is intended to determine how universities like Penn can help address these pressing humanitarian challenges, respectively summarized by the terms access gap and research gap. In both cases, major research institutions are well-positioned to make a difference. Penn scientists are often major contributors in the development of health-related innovations. At the same time, Penn has an avowed commitment to advancing the common public good. As members of this University, we must hold ourselves to this commitment by conducting socially responsible research and management of intellectual property.

In targeting the access gap, we outline potential licensing solutions that would ensure access to Penn's innovations in resource-limited countries. We argue that any such solution should have three key features: (1) it must be put into place prospectively, at the time of initial out-licensing; (2) it must include an evidence-based mechanism for bringing about price reductions for medicines in poor countries; and (3) it must center on universities and their role in the biomedical research enterprise. We propose model licensing language, known as the Equitable Access License, that we believe fulfills these criteria. Concurrently, we call upon Penn to address the research gap with an increased emphasis on the study of neglected diseases. For example, Penn could take steps to open up our portfolio of research innovations to public-private partnerships developing drugs for neglected diseases. By becoming a leader in neglected disease research, Penn could also gain access to a growing pool of nontraditional funding sources. Underlying these specific proposals to address the access and research gaps is a fundamental shift in judging the success of technology transfer: not just by revenue earned and licenses executed, but by contribution to the improvement of global human welfare.

These policy changes have the potential for significant impact on patient populations in the developing world. As evinced by the HIV pandemic, opening select pharmaceutical markets to generic competition—as would be achieved by something like the Equitable Access License—dramatically decreases drug prices and improves disease outcomes. Health care workers treating neglected diseases are anxiously awaiting novel treatments that are safer and more effective. Meanwhile, if implemented carefully and thoughtfully, the changes suggested here need not interfere with Penn's ability to work with private entities, either as funding sources or developers. These proposals come at a time when Penn actively seeks to enhance its international presence through global engagement. We believe our ideas offer Penn an opportunity to reinforce and advance its role as a leader among universities and reaffirm its dedication to the global public good.

● 2. PROBLEM STATEMENT ○

Approximately ten million people die needlessly each year because they do not have access to existing essential medicines and vaccines.¹ This access gap stems from several factors, including unreliable healthcare delivery systems, lack of political will for public financing of healthcare, and high prices for medicines.² These factors are mutually reinforcing, particularly in poor countries. While third-party medical insurance often insulates patients in wealthy countries from the high cost of medicines, patients in poor countries are often not as fortunate. On average, these patients pay more than seventy percent of medicine costs themselves.³

High prices result in large part from the temporary monopolies granted to pharmaceutical companies through patent and regulatory systems.⁴ In fact, the introduction of generic competition may be the most important factor in lowering prices in a given country.⁵ Importantly, there is little reason to expect that increased generic competition in poor countries would significantly impact the revenues of pharmaceutical companies and thereby impede future innovation. The branded pharmaceutical industry in the United States derives only five to seven percent of its profits from all low- and middle-income (LMI) countries.⁶

Some authors have argued that pharmaceutical companies are unlikely to patent in poor countries and thus intellectual property protection has little to do with the access gap.⁷ Yet there is widespread evidence that pharmaceutical companies do seek patents in poor countries.⁸ For instance, many of the most important antiretrovirals for HIV treatment are widely patented in Africa.⁹ Moreover, the presence of patents in one developing country may affect access to generics in countries where no patents exist, as developing countries differ substantially in terms of their capacity to produce medicines.

International trade policy has further exacerbated the access gap. India passed legislation this March to comply with the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, jeopardizing the world's most important supply of generic medicines. The United States continues to exert pressure on developing countries outside of the WTO framework by imposing so-called "TRIPS-plus" standards on these countries in its bilateral free trade agreements.¹⁰ These standards extend monopoly rights for medicines and make it more difficult for governments to promote generic competition or to import generic drugs from other countries.

In addition to the inequitable distribution of existing pharmaceutical technologies, disparities in funding allocation for research and development further limit treatment availability for developing-world indications. Countless people suffer from neglected tropical diseases, such as African sleeping sickness, lymphatic filariasis, and blinding trachoma. Drug companies lack the financial incentive to develop medicines for these diseases because the afflicted populations are unlikely to be able to afford them. Therefore, these conditions have failed to attract research investments from the branded pharmaceutical industry. Indeed, it is estimated that only 10% of the world's health research funds are devoted to the diseases that are the predominant health burden for 90% of the world's population.¹¹ This lack of financial investment has led to a significant missed opportunity to develop novel treatments. From 1975 to 1999, only 16 of the 1393 new drugs that came to market were designed to treat neglected diseases.¹² As a result of this research gap, safe and effective treatment options are extremely limited.¹³

2.1 The Role of Universities

Research universities have a unique opportunity to address both the access and research gaps via their research policies and licensing agreements. Multiple studies have confirmed that university research is vital to the development of new medicines.^{14,15,16} The University of Pennsylvania has consistently ranked second nationwide in funding received from the National Institutes of Health; in fiscal year 2004, total research funding was \$756 million.¹⁷ Meanwhile, the institutional principles of the University are well-aligned with the goal of improving access to medicines globally. Our strategic plan mentions the goal of improving "the quality,

impact, visibility, and translatability of Penn's academic research and scholarly activity."¹⁸ Penn's Center for Technology Transfer explicitly states that its chief objective is to "commercialize Penn research discoveries for the public good."¹⁹ This stated goal has direct implications for how the University should use its leverage in licensing negotiations to ensure that the University of Pennsylvania's ingenuity and infrastructure are utilized to maximize global welfare.

Penn would not be alone in considering creative solutions to the problem of limited access to medicines in the developing world. Several ideas have circulated in academic and policy circles over the past few years. For instance, a 2005 report published by the American Association for the Advancement of Science explored ways to license university discoveries to drug companies in a way that ensures that the drugs can be accessed for humanitarian uses.²⁰ The report argued that humanitarian licensing practices would involve "a provision in a license whereby inventors and technology suppliers protect in advance the possibility of sharing their proprietary technology with third parties for the benefit of people in need." The Association of University Technology Managers (AUTM) has convened a group known as Technology Managers for Global Health to look at how university research can be optimally advanced to improve global health outcomes.²¹ Proposals for universities to institute policies which would promote neglected-disease research have also been put forth.²²

Despite this lively scholarly discussion, no university has incorporated "humanitarian" licensing provisions into its intellectual property policy to date. Progressive technology transfer for neglected diseases has also been slow to move beyond isolated deals. Therefore, we are interested in determining how research universities like Penn might best address the access and research gaps in a systematic yet feasible way.

In this paper, we provide evidence that Penn is ideally situated to play a leading role in addressing both the access and research gaps. We hope to capitalize on: (1) the University's avowed commitment to global engagement and the advancement of the public good; and (2) its upstream position in developing novel biomedical end products. In the 2005 Penn Compact, the University presented its vision for Penn's growth in the 21st century. The document describes Penn's aspiration to "engage dynamically with communities all over the world to advance the central values of democracy and to exchange knowledge that improves quality of life for all."²³ We wholeheartedly support this vision, and believe that Penn should draw on the strengths of its research enterprise in order to realize it. Specifically, we encourage the University to look for ways that its research activities, particularly those in the biomedical sciences, can be harnessed to improve human welfare around the world.

As one of the world's premier research institutions, Penn is already a center for discoveries with significant global impact. However, we strongly believe that Penn's responsibility for those innovations does *not* end at licensing them out for further development under traditional licensing policies. The University has the opportunity to institute intellectual property policies which would ensure that its innovations reach those who need them most. If carefully developed, such policies need not interfere with Penn's ability to work with private entities, either as funding sources or as downstream developers. Secondly, we propose several measures to address the research gap – including amending research policy to reflect this priority and seeking out nontraditional partners in technology transfer deals. Clear and sensible policies on intellectual property and the promotion of neglected disease research would elevate Penn's reputation as a trailblazer in addressing one of the most challenging humanitarian crises of our time.

● 3. SPECIFIC PROPOSALS ○

3.1 Addressing the Access Gap – The Equitable Access License

International guidelines on intellectual property play a clear and significant role in increased prices for pharmaceuticals worldwide. However, given the current international political climate, systemic reform of intellectual property protection seems unlikely to occur in the near future. Therefore, we propose a modest intervention that works within existing trade-law and drug-development paradigms to circumvent both national

and international obstacles to generic medicine production. Our proposal, known as the Equitable Access License, has three key features: (1) it is prospective in scope, (2) it facilitates unfettered generic competition in poor countries, and (3) it centers on universities and their role in the biomedical research enterprise. Briefly, an EAL uses a self-enforcing mechanism to allow any party to manufacture and distribute the licensed technology and any derivative products in poor countries, while minimizing administrative overhead and political uncertainty.²⁴

3.1.1 The open licensing approach

The ultimate goal of this proposal is to achieve marginal cost pricing for health-related end products, including medicines and medical devices, in low- and middle-income (LMI) countries. To achieve this, we propose that universities' technology transfer agreements facilitate generic competition by providing open licenses guaranteeing third-party manufacturers the right to compete in LMI markets, regardless of patents or other forms of exclusive rights.

While a 'fair pricing' approach—obliging the original manufacturer of a medicine to make it available at a low markup on marginal cost of production—might seem like a plausible (or even preferable) alternative to an open licensing approach, it would require a credible threat of enforcement for breach of contract. The open licensing approach, on the other hand, does not require universities to take an active role in monitoring or enforcement. It achieves this by introducing third parties (generics companies) with market incentives to narrow the access gap by offering low-priced, but still profitable, products.

The open licensing approach may also provide patients in LMI countries with less expensive medicines than the fair pricing approach would. The balance of the evidence indicates that competition has been more a more reliable method of lowering prices than voluntary "at cost" pricing.²⁵ For example, although Bristol Myers Squibb agreed in 2001 to sell its antiretroviral stavudine below cost in Africa, generic companies were able to undercut its prices by almost seventy percent, presumably while still turning a profit.²⁶

Finally, the open licensing approach has the advantage of fostering a more sustainable and locally appropriate supply of low-cost medicines in developing countries. By capturing a small but meaningful market, generic developers would be able to attract the investment necessary to sustain their low-margin business. Our proposal would also allow third parties to modify and to improve their products for the particular needs of target countries such as fixed-dose combinations and pediatric dosing.

3.1.2 Applicable technologies and territories

To be appropriate for an Equitable Access License, a technology must be health related. The approach should be well suited to a wide variety of technologies, from small-molecule drugs and macromolecules to diagnostic and manufacturing tools. The most obvious candidates are potential pharmaceutical products, both small-molecule drugs and biologic therapies. We contend that, in order to meet the health needs of patients in developing countries, EAL provisions must apply to all low- and middle-income countries (as defined by the World Bank) and must include the right to supply the private sector in these countries.²⁷

3.1.3 Mechanism of the EAL

The mechanism of operation for the EAL can be summarized in three steps: (1) cross-licensing and grant back of rights between the university and a licensee; (2) notification by a third party of intent to supply an LMI market, triggering the provisions of the EAL; and (3) grant back of rights for any subsequent developments made by the third party to the university. This grant back ensures that the EAL still applies to biomedical end products that combine several licensed innovations, as is frequently the case. These steps are outlined schematically in Appendix 1; model licensing provisions have been included as Appendix 2.

The first step is essentially an exchange of licenses. Just as with a normal exclusive licensing transaction, the university grants the licensee rights to a particular innovation. This agreement will likely include, at a minimum, exclusive rights to implement the university's technology in high-income countries. In exchange, the licensee will "grant back" to the university a set of rights referred to as "associated rights"; this would include all of the potentially exclusive rights the company holds or acquires that could prevent a third party from producing or delivering an end product. The EAL's provisions must apply to any technologies necessary to the production of the end product even if those technologies are not directly related to the university's innovation.

However, the grant back would not include any material property—such as cell lines—possessed by the original licensee or sub-licensees. Importantly, the EAL's provisions are designed to apply not only to the initial licensee but also to any subsequent sub-licensees. This becomes relevant because the initial license may be with a biotech company, which will sublicense the university technology to a pharmaceutical company only after further development. The university obtains these rights for the sole purpose of granting an automatic sub-license to any third-party manufacturer, thereby ensuring freedom to operate in LMI countries. This type of grant back arrangement is not without precedent. The Bill & Melinda Gates Foundation has included similar clauses in the global health grants of its Grand Challenges Initiative.²⁸

The second transactional element of the EAL is a simple notification procedure: a third party notifies both the university and the original licensee that it intends to make, use, or sell the end product in an LMI market. We anticipate that there will be three main types of third-party notifiers: (1) generic companies that wish to produce or sell in an LMI country; (2) government agencies or non-governmental organizations (NGOs) that wish to import generics from a third party; or (3) researchers who wish to make improvements on an end product to adapt it to a developing country's needs. In order to foster an open and competitive environment, the EAL permits multiple notifiers. Upon notification, the university's licensed rights, including associated rights from the licensee, flow to the third-party manufacturer. Through this contractual flow of rights, patent, regulatory, and manufacturing barriers are lifted for the notifying entity.

In keeping with the spirit of the Bayh-Dole Act, the EAL requires notifier(s) to pay a small royalty to both the university and the original licensee. This has the added benefit of offering a revenue stream to all parties implementing the EAL. For low-income countries, we propose that the royalty be set at a rate within the range recommended by the United Nations Development Programme of zero to six percent of sales.²⁹ For middle-income countries, we propose a flat rate of about five percent. The license will have to establish an equitable division of royalties between the university and the licensee.

The EAL also permits notifiers in any country to engage in research to improve an end product. For example, a notifier may seek to adapt a technology to local circumstances. The final step of the EAL licenses any such improvements back to the university for the sole purpose of sublicensing them under the EAL's terms. In other words, any improvements made by a notifier would themselves be subject to the terms of the EAL. The notifier would receive royalties for the use of its improvements in LMI markets, but it would not be able to prevent others from utilizing these improvements.

3.1.4 Alternative Approaches

The problem of the access gap has attracted attention from a number of interested parties. While various proposals have been debated, no systematic solution has been agreed upon. Two such proposals, compulsory licensing and voluntary differential pricing, are examined in turn:

Compulsory licensing: This proposal allows the governments of WTO member countries to issue their own licenses for production of specific medicines. This right is governed by international law under the agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS).

While compulsory licensing would certainly be an advance in trying to close the access gap, there are several drawbacks to this approach. First, rather than taking on the broad access gap in a consistent and systematic way, compulsory licensing works on a case-by-case basis that necessarily introduces burdensome bureaucratic hurdles. Such an approach requires substantial political will on the part of individual governments to effect top-down change. In many of the countries where medicines are most needed, such political will and responsibility are markedly absent. For example, leaders in South Africa, India, and China have all at times gone so far as to deny the existence of HIV/AIDS in their respective countries.

In addition, formal and informal pressures exerted by industrialized nations, particularly the United States, impede the ability of developing countries to pursue compulsory licensing as a solution. The efficacy of compulsory licensure is limited by the concurrent international political milieu. For example, the United States is currently using free trade agreements to negotiate TRIPS-plus standards that restrict a nation's ability to invoke a compulsory license.³⁰ In the absence of a systematic approach to open licensing, disputes have erupted between nations trying to protect their biomedical industries.

By contrast, the EAL aims to avoid these bureaucratic and political obstacles by establishing clear guidelines *a priori* to govern eligibility for open-access licenses in a manner that safeguards exclusive patents in industrialized nations.

Voluntary differential pricing: Voluntary solutions, on the other hand, would shift the onus from governments to the pharmaceutical companies. Unfortunately, voluntary differential pricing has not proved forthcoming.

Voluntary licenses for HIV antiretrovirals remain few and far between, to say nothing of medicines for diseases that garner less political attention. Even in the few cases where voluntary discounts have been achieved, they resulted in prices that typically remain above the lowest price for generic versions.³¹

For example, one specific proposal calls for a voluntary discount regimen governed by confidential negotiated rebates between pharmaceutical companies and country governments.³² Even if pharmaceutical companies agreed to such a solution, in practice it would be neither systematic nor transparent. That is, each medicine would have to be negotiated for each country on a case-by-case basis—and those negotiations would not be subject to public scrutiny, which has been the only effective tool in bringing about true voluntary concessions. Perhaps most importantly, the problem with this type of voluntary solution is that no pharmaceutical company has displayed a willingness to implement it.

In contrast, the EAL relies instead upon the initiative of entities with greater incentive to make medicines available in developing world markets – generics manufacturers themselves. Rather than rely on case-by-case good will gestures, which have been disappointingly rare, the EAL enables participation by third parties in markets where branded pharmaceuticals have not adequately responded to the substantial need.

This is not to say that the EAL is the only proposal with the potential to diminish the access gap. However, in considering alternatives, we emphasize that the solution must: (1) be put into place prospectively, at the time of initial out-licensing and (2) include an evidence-based mechanism for bringing about price reductions for medicines in poor countries. Our research suggests that the EAL best fulfills these criteria.

3.2 Addressing the Research Gap – Neglected Disease Proposals

While the above proposals are designed to enhance access to medicines with a sufficient market to induce development, we also foresee a role for universities in addressing the research gap. We advocate specific policy changes intended to advance the development of drug treatments, prophylaxis (including vaccines), and devices for neglected diseases. Neglected diseases include those for which treatment options are inadequate or do not exist, and for which drug-market potential is insufficient to attract private sector investment. More formally, we have adopted a classification method from the FDA Orphan Drugs Act: “a neglected disease (ND) is any

disease, condition, or affliction that either affects less than 200,000 persons in the United States or for which there is no reasonable expectation that the cost of developing and making available in the United States a treatment, prophylaxis, or device for such disease, condition, or affliction can be recovered from product sales in the United States.”³³ The University of Pennsylvania should consider the following policy changes designed to support and promote ND research:

3.2.1 Reevaluating Technology Transfer Success

Penn’s Center for Technology Transfer explicitly states that its chief objective is to “commercialize Penn research discoveries for the public good.”³⁴ If the University is to remain true to its stated mission, we can no longer judge the success of technology transfer based solely on revenue generated through licensing. Accordingly, we believe that the University, in evaluating the success of technology transfer, must make potential for the improvement of global human health a primary consideration. This commitment should be formalized by changing the language governing the expectations of technology commercialization at Penn.³⁵ We believe that the policy should include a clause stating that the CTT mission is “Primarily, to improve global human welfare through technology transfer.”

Peer institutions such as the University of California at Berkeley are already making such a commitment. Carol Mimura, associate director at Berkeley’s Office of Technology Licensing states, “In the new reality, we can have a double bottom line. We can have the financial bottom line, and we can have the societal-impact bottom line. And they’re equally important to us. On that basis, we can employ a full spectrum of IP-management strategies, not just the few that focus on royalty revenue. Under double bottom-line concepts, societal good has a value. It’s just not the same as bringing in dollars under a running royalty from a license. And it fulfills our mission of public service.”³⁶ Maria Freire, former Director of the Office of Technology Transfer at the National Institutes of Health (NIH), has also publicly endorsed this concept, emphasizing a moral imperative in an editorial entitled, “Technology Transfer’s Next Frontier: Global Health as a New Bottom Line.”³⁷

Mimura has shown a commitment to this belief; Berkeley’s three-year-old Socially Responsible Licensing initiative has so far led to more than ten separate agreements aimed at enabling Berkeley researchers to translate the fruits of their research to the developing world. Upon altering its technology transfer metrics in a similar manner, Penn too could reap the benefits of progressive partnerships, additional funding, and enhanced visibility at the forefront of global health.

3.2.2 Marketing Neglected Disease Research Capabilities

Penn should promote its position as a leader in ND research, and, in so doing, should seek to attract nontraditional partners and funding for ND research from non-profit grant sources, public-private partnerships (PPPs), and pharmaceutical firms. Example interactions include: patent donation, dual-market licensing, and straightforward exclusive/non-exclusive licensing. Public-private partnerships, such as the Medicines for Malaria Venture, and new funders like the Bill & Melinda Gates Foundation are addressing the development gap, pushing an unprecedented number of compounds through clinical trials. However, these projects depend on universities and other scientific institutions to fill the discovery gap. Therefore, it is essential that we seek out new ways to encourage work in these areas.

The burgeoning field of public-private partnerships for global health research has attracted over \$1.2 billion in funding from sources such as the Gates Foundation, the vast majority of which is contracted out to research scientists.³⁸ Penn should ensure that its scientists are not excluded from benefiting from these nontraditional sources of ND funding. Universities commonly cite an insufficient indirect cost rate as a reason to discourage grants from these sources. We call upon Penn to work in conjunction with other research universities to collectively find ways around this issue. Penn should also remove barriers to research agreements with PPPs; this process should include a critical appraisal of the Guidelines on Foundation Intellectual Property Issues –

its necessity, its purpose, and potential negative effects it may have in regards to securing nontraditional funding.³⁹

Several of Penn's peer institutions have had marked success with nontraditional partnerships:

1) UC Berkeley/Amyris/IOWH for Microbially-Produced Artemisinin: In 2004, UC Berkeley issued a royalty-free license for microbially-based production of artemisinin. This was the 4th such license executed by the school's Socially Responsible Licensing Initiative. Currently, artemisinin is an essential treatment for resistant malaria around the world. Unfortunately, the agriculturally-produced compound is in limited supply, and demand is only increasing. For example, total doses consumed increased from 100,000 in 2001 to 60 million in 2005.⁴⁰ Novel production methodologies, like that proposed by Berkeley, will be essential to the fight against malaria in coming years. UC Berkeley has licensed its technology to two entities – the Institute for One World Health, a non-profit pharmaceutical company that will conduct non-clinical regulatory work necessary for approval, and Amyris, a biotech company that will produce the drug at-cost. The project is being funded by a \$42.6 million grant from the Bill & Melinda Gates Foundation.⁴¹

2) University of Nebraska/Medicines for Malaria Venture/Ranbaxy Laboratories
In 2003, Medicines for Malaria Venture negotiated a deal by which the University of Nebraska offered a royalty-free license to Ranbaxy Laboratories to develop and produce an anti-malarial compound derived from wormwood.

3) Yale University/University of Washington/Institute for One World Health dual-market license for anti-Chagas compound

In 2003, Yale and University of Washington licensed azoles, a new class of anti-parasitic compounds, to the Institute for One World Health. The license allowed IOWH to develop azoles for developing-world applications only. Therefore, the universities reserved the right to issue a new license for developed-world applications, most likely to a for-profit venture. IOWH will test azole activity against Chagas disease, a parasitic infection that afflicts 16 to 18 million people each year.⁴²

3.2.3 Neglected Disease Research Exemption

In the above cases, the innovations potential applicability to neglected diseases was apparent at the time of university licensing. However, this is not always the case. In order to ensure that licensed innovations remain available for ND drug development, universities should create a research exemption for neglected diseases, retaining all intellectual property rights for the purpose of ND research. This would open up the intellectual property for ND research at any academic institution. For innovations which have been patented but not yet out-licensed, Penn should allow other non-profit institutions to conduct research—including commercial research—for neglected diseases using the University's patented innovation. Penn should seek to transfer materials and know-how related to patented innovations for this purpose and should not require that any royalties from resulting ND end-products or subsequent ND-related improvements be paid to the University. Further, for any innovations that Penn out-licenses, the University should retain the right to non-exclusively license use of its technology for research on neglected diseases anywhere in the world and for distribution of resulting products in LMI countries. In inserting such a clause into its licensing agreements, Penn would assure the freedom to exploit any eventual product resulting from the licensed technology in LMI countries.⁴³ In addition, the University would retain the right to transfer its materials and know-how related to the out-licensed intellectual property to any institution researching a neglected disease, and, where possible, would capture all licensee improvements on the University's technology into the open licensing pool.

Some have objected to the proposed research exemption for neglected diseases, worrying that such open access to IP would threaten existing licenses for non-ND applications. We argue that this objection is unfounded, as use of IP for non-neglected diseases would be illegal and would constitute an actionable infringement. The key question, then, is whether ND research can be easily distinguished from non-ND research. In the majority of

cases, these distinctions would be clear, and infringement would be apparent at the point of registration with a regulatory agency. For less clear-cut cases where registration information is not actionable, infringement may be less feasible to prove. However, these cases would be murky with or without the research exemption – in other words, this exemption does not exacerbate that situation.

3.2.4 Incentives for Neglected Disease Research

Universities, including Penn, should seek to strengthen their ND research program by placing a premium on potential for contribution to ND research during the process of hiring new faculty. Furthermore, they should recognize the difficulty of translating basic science research into end products in considerations of faculty promotion; hence, the University should develop alternative methods for evaluating ND researchers that extend beyond publications authored and grants received. Finally, the University should encourage ND researchers' participation in preclinical development projects for neglected diseases, particularly open-source initiatives seeking to pool research resources for the purpose of speeding commercialization [e.g. Tropical Disease Initiative and Biological Innovation for Open Society.]

3.2.5 Formalizing Annual Review Practices

In addition to its normal research monitoring activities, Penn should separately and specifically track progress of any research that falls under the ND rubric. The University should continuously evaluate all of its research activities—not just its ND portfolio—for new or currently shelved technologies with promising potential for application to ND end product development.

● 4. IMPACT ESTIMATE ○

4.1 Impact on Patients in Low- and Middle- Income Countries

The impact of these proposals on patients in low- and middle- income countries is largely dependent on the University's ability to develop novel drugs, diagnostics, or devices useful in treating human disease. A recent review indicated that the ownership position of universities as a whole in pharmaceutical technologies is both substantial and increasing.⁴⁴ Both the number of patents and, concomitantly, the number of license agreements executed by universities have approximately doubled between 1993 and 2003.⁴⁵ A major share of this university intellectual property is in the biomedical field.⁴⁶ For example, universities own patent rights in key pharmaceuticals used in recent years, including the cancer drugs cisplatin and carboplatin,⁴⁷ pemetrexed (Alimta),⁴⁸ cetuximab (Erbix);⁴⁹ the anemia treatment epoetin alfa (Eprex);⁵⁰ the AIDS drugs zalcitabine (Zerit),⁵¹ lamivudine (Epivir),⁵² abacavir (Ziagen),⁵³ emtricitabine (Emtriva),⁵⁴ and T20 (Fuzeon);⁵⁵ and the best-selling glaucoma medicine latanoprost (Xalatan).⁵⁶

Penn's role as one of the foremost research institutions in the nation suggests that it too will play a significant role in globally relevant discovery. An annual research budget of \$756 million and world-renowned faculty provide the necessary substrates for discovery. Furthermore, Penn has renewed its dedication to translating basic science research to biomedical end products. For example, Scott Diamond of the Penn Center for Molecular Discovery has received a significant grant from the National Institutes of Health to conduct high-throughput screening for novel drug candidates.⁵⁷ The Pharmacology Department, led by Garret Fitzgerald, has created the Institute for Translational Medicine and Therapeutics to focus on new and safer therapeutic entities.

The University's recent research initiatives have already begun to reap dividends. A simple survey of the Center for Technology Transfer reveals hundreds of disclosures, many of which have clear implications for the treatment of diseases with a significant global health burden.⁵⁸ Titles of currently available technologies include "Treatment and Prevention of Plasmodium falciparum Malaria," "Method of Diagnosing Alzheimer's disease,"

and “Novel HIVs useful in Vaccine Development and HIV Drug Design.” Furthermore, Penn immunologist Dr. Mark Greene’s research underlies a first-line monoclonal antibody treatment for HER2-positive metastatic breast cancer known as Herceptin (Trastuzumab). In 2005 alone, the treatment generated \$747 million for its maker, Genentech.⁵⁹ While such biologic agents pose unique challenges in application to resource poor settings, the success of Herceptin is a testament to Penn’s potential to be a leader in biomedical innovation.

Recent initiatives that promote generic competition within low- and middle- income (LMI) countries have proven extremely effective in lowering the price of essential medicines.⁶⁰ For example, when the Brazilian government began generic production of antiretrovirals in 2000, prices quickly fell by 82%.⁶¹ A precedent exists for universities playing a role in engendering generic competition. In 2001, the humanitarian organization Médecins Sans Frontières (MSF) requested a license from Yale University to buy generic stavudine – an HIV medication – from an Indian company which had offered to sell it in South Africa for approximately three percent of the price of the branded version.⁶² Though Bristol-Myers Squibb (BMS) had an exclusive license to sell the drug, Yale was the key patent-holder.⁶³ Within weeks of receiving the request from MSF, Yale and BMS announced that they would permit the sale of generics in South Africa and that the price of brand-name stavudine would be slashed thirty-fold for the government and for non-governmental organizations.⁶⁴

The impact of this intervention was unequivocal: rapid expansion of HIV-treatment programs in sub-Saharan Africa would not have been possible without generic stavudine, a WHO-recommended first-line therapy. Prices fell almost immediately from \$1600 to \$55 per patient year for the branded version, down even further (to \$35 per patient year) with generic competition.⁶⁵ While a success story in many ways, the change in policy agreed to by BMS occurred retrospectively and only with great public pressure. Had access-minded licensing provisions been in place *ex ante*, these difficulties would have been avoided and an untold number of lives could have been saved.

The precise impact of a university licensing intervention in improving access remains difficult to appraise. Essentially, this is a problem of measuring missed opportunities. While one might argue that it is difficult to point to cases where university licensing was the limiting factor in expanding access, this misses the crux of why licensing is important. University licensing presents an *opportunity* for increasing access. This opportunity arises because universities lie far upstream in the drug development process and because universities respond to a different set of incentives than companies.

Furthermore, the critical moment for taking advantage of such an opportunity has not passed. While case-by-case negotiations (e.g., Medecins Sans Frontieres and Yale with stavudine and the Clinton Foundation with a number of other antiretrovirals) have brought down the prices for first-line HIV treatment, the underlying problem was not resolved. For this reason, we are seeing a ‘second-line crisis’ in the price of next-generation antiretrovirals that overcome growing resistance profiles and have lower toxicity than first-line drugs.⁶⁶ These second-line medicines will soon become mainstays of antiretroviral therapy—for example, Emory’s emtricitabine will be recommended as a first-line therapy in the latest WHO revision of treatment guidelines.⁶⁷

While global health proponents have traditionally focused on tropical and other infectious diseases, Universities must acknowledge the potential of university licensing in helping to curb morbidity and mortality caused by non-communicable diseases in developing countries. Chronic conditions, not just infectious diseases like HIV, afflict the developing world as well. In fact, as highlighted in a recent series in *The Lancet* entitled “The neglected epidemic of chronic disease,” of the 35 million deaths that will occur in 2005 from chronic diseases, 80% of them will take place in LMI countries.⁶⁸ By considering both infection and noninfectious illnesses, universities can play a critical role in lessening the overall disease burden in these populations.

4.1.1 *Selecting Markets for Segmentation*

The selection of territories for this sort of market segmentation will, at some point, be an arbitrary one. The theoretical optimum would be “Ramsey pricing,” such that all prices are set on an individual basis according to

relative income.⁶⁹ This is clearly not feasible, but it highlights the fact that any workable system of differential pricing will have to choose some parameters to demarcate categories.

The only feasible way of demarcating categories is by country because of irreducible legal and regulatory frameworks in place within countries. A category of developing countries based on overarching national economic indices could be used to establish a market where true generic competition would reduce prices. We believe the most sensible category would include all low- and middle-income countries as defined by the World Bank.⁷⁰

We include middle-income countries because many of these countries (e.g., Brazil, Mexico, and South Africa) have highly unequal income distributions and large poor populations that must obtain their own care in the private sector.⁷¹ For example, 613 million people in China live on less than \$2 per day.⁷² If licenses only enabled generic companies to enter low-income markets, they would leave out many individuals whom universities aim to benefit. Those middle-income countries that do grow sufficiently to be recognized as high-income countries would no longer be subject to the license. Finally, it should be made clear that any entity that wishes to supply an LMI market—even a company based in a high-income country—would be able to do so under the EAL.

The revenue potential of middle-income countries would help ensure that there are sufficient financial incentives for generic companies to sustain production of a given medicine. Additionally, excluding middle-income countries would prevent equitable access provisions from operating where they might work best—for the often chronic, developed-world indications in the developing world. Middle-income countries are in particular need of such medications.⁷³

4.2 Impact on the University of Pennsylvania

Recognized as America's first university, the University of Pennsylvania has served as a model in education, public service, and research enterprises since it was founded in 1751. In recent years, the University has rededicated itself to its global mission. A Task Force on Global Engagement was commissioned by President Amy Guttmann in 2005 to consider creative ways to transform its stated goals into action. We believe that adopting the above proposals is consistent with Penn's desire to remain a leader amongst universities with international spheres of influence. Furthermore, the University is likely to derive a substantial public relations boost for its efforts to address the global lack of access to medicines.

4.2.1 The Need for Collective Action

As with any new and innovative approach to technology transfer, Penn may hesitate to be the first to change their licensing practices due to concerns that industry might shy away from a solo actor. It is therefore critical that major research institutions work together to bring these new approaches forward. The ultimate goal is for all universities involved in biomedical research to collectively adopt access-minded licensing practices, thereby maximizing impact and bargaining power with industry partners. This will only happen with strong leadership of eminent, globally engaged universities. In addition to leading the way through its own policies, specific venues at which Penn could promote collective university action include the biannual meetings of senior research officers at major research institutions, and the Association of University Technology Managers (AUTM).

This movement is already occurring to some extent, and Penn would not be alone in pushing things forward. Many universities have negotiated individual access-minded licensing agreements, and others have begun to alter their broader approach to research and development. For example, the University of California-Berkeley has recently (October 2005) begun marketing its 'Socially Responsible Licensing Initiative' as a way to attract nontraditional funding and has already signed a handful of deals with foundations and nonprofits under that

licensing rubric.⁷⁴ It is to Penn's advantage, both from a global health and a public relations perspective, to play a catalytic role in the widespread adoption of these policies.

4.2.2 University- Industry Relations

When entering into early negotiations, it will be important to keep in mind that our industry partners are not averse to tackling global health problems. Indeed, many pharmaceutical companies are outspokenly committed to improving global human welfare.⁷⁵ However, the lawyers dedicated solely to contract negotiation are not necessarily the most appropriate representatives of pharmaceutical companies' priorities. Top scientists and CEOs may be more likely to value advancement of global health, especially considering the interest in repairing the industry's public image. Penn has superb relationships with industry leaders and is well-suited to start this dialogue. Through engaging appropriate actors and acting in concert with other leading research universities, Penn's ability to adopt innovative licensing policies increases significantly.

4.2.3 Economic Impact

The stated mission of the University of Pennsylvania's Center for Technology Transfer is to "commercialize Penn research discoveries for the public good." While we strongly emphasize the great potential for a positive impact around the world under Equitable Access Licenses (EAL), we recognize that the university is also concerned about its obligation to continue creating and disseminating new knowledge through its ties to industry. The revenues gained from technology transfer are used to re-invest in research and are critical to ensure that new advances are quickly developed into technology that will improve quality of life. In order to estimate the impact of an EAL policy, we have created a conservative financial model that yields possible yearly financial losses incurred due to excluding LMI country markets from possible revenues. We also explore the possibility that biotechnology and pharmaceutical companies may attach lower value to patents with an EAL provision that are passed onto the university in the form of lower royalty percentages. The results of our preliminary Discounted Cash Flow Analysis, the details of which have been included in Appendix 3, indicate that the Net Present Value of lost royalties will represent less than 0.02% of the University's annual budget. We firmly believe that the actual loss will be even lower than the numbers currently quoted in our conservative assumptions. We hope to work closely with the Center for Technology Transfer to develop an even clearer picture of how much the University's bottom line will be impacted by the adoption of our proposals.

4.2.4 Special Cases

While the EAL has broad applicability to a number of disease states, it is important to identify products that might lie outside of its scope, including vaccines, medical devices and specific indications. These cases are carved out for a simple practical reason: we believe that alternative mechanisms would speed discovery and access for these applications.

Vaccines: The vaccine market worldwide earns over \$7B in annual revenue (15% from Wyeth's blockbuster Strep pneumococcus vaccine, Prevnar⁷⁶). It is important to note that this is a large volume market, and a large proportion of volume is directed to low income, low profit markets. Developed countries in Europe and North America purchase roughly 10% of doses, but represent over 70% of market revenue. Developing countries, supplied chiefly through UNICEF, receive over 40% of doses, but they collectively represent less than 5% of revenue.⁷⁷

The economic reality of this market, coupled with liability concerns and high manufacturing costs (manufacturing fixed costs represents roughly 60% of the expenditure per dose⁷⁸), have led many pharmaceutical companies to exit the market. According to Patricia Danzon, "In 1967 there were twenty-six licensed manufacturers of such vaccines; in 2002 there were only twelve."⁷⁹ High cost of development exacerbates this situation – FluMist's pre-approval costs totaled between \$500 and \$750M.⁸⁰

Given the market's relative fragility and the vital importance of its survival (vaccines for Hepatitis B and Haemophilus influenzae alone saved over 670,000 lives between 2001 and 2003 alone),⁸¹ we believe that vaccines would be better addressed through mechanisms other than the EAL. These mechanisms might include our ND proposals that support participation in public-private research partnerships and advocacy to increase funds for organizations like UNICEF and the Vaccine Fund.

Biologics and Medical Devices: While the EAL could be applied to these classes of products, many require specialized production capabilities and expertise that generics manufacturers are unlikely to possess. Therefore, insertion of the EAL will likely do little to improve access to these innovations. Where technology transfer to generics companies is possible, we would encourage use of the EAL. Where use of generics licensing seems infeasible or ill-advised, we would encourage use of other tools, including engagement in public-private partnerships focused on such products (e.g. the Foundation for Innovative New Diagnostics).

Special Indications: In general, diseases with significant population impact like AIDS, TB and Malaria would fall outside of the neglected disease definition outlined above. Given the potential to market these products in developed countries (for infected individuals and/or traveler's markets), we believe that the EAL would provide a useful tool to promote access. However, there are important exceptions to this rule – namely, specific subpopulations within these disease categories. For example, pediatric or end-stage AIDS patients would fall outside of the EAL, and be addressed by neglected disease proposals instead.

4.3 Impact on Pharmaceutical Companies

As stated above, sales in low- and middle-income countries represent a small proportion of pharmaceutical industry revenue – 5-7% on average.⁸² Sub-Saharan Africa represents only 1.3%. A former CEO of Eli Lilly put this in perspective, stating that complete loss of this market would cost “about three days fluctuation in exchange rates.”⁸³ We should also note that we are proposing competition in these markets, not withdrawal.

4.3.1 Diversion

One potential concern with the market segmentation created by the EAL is the potential for diversion of drugs from poor countries for illicit resale in rich countries. Historically, however, diversion from poor countries has rarely been observed. Generic drugs have been produced in India for decades without apparently infiltrating or undermining Western markets.⁸⁴ Meanwhile, the only significant media reports of diversion have been shown to be overblown. For example, GlaxoSmithKline alleged in 2002 that 36,000 packages of HIV medicines worth approximately \$18 million were found to have been diverted from a charitable initiative in West Africa to the EU.⁸⁵ It turned out that 99% of the packages handled by the parallel trader were not part of Glaxo's charitable access initiative but rather ordinary commercial sales at prices approximating EU prices. Also, Glaxo did not label the packages as ineligible for sale or re-importation in the EU.⁸⁶

Insofar as diversion is a concern, it can be addressed in the same manner that the World Trade Organization has—by requiring use of different packaging, pill color, and pill shape in different countries to facilitate the identification of illegal imports.⁸⁷ The equitable access approach actually reduces the risk that medicines would be diverted to markets in high-income countries compared to a drug-donation or voluntary differential pricing approach. Differentially-priced products sold by the original, branded company (as in Canada) may be susceptible to parallel trade, particularly if they are similar in appearance. Regulatory barriers exist to prevent these medicines from entering high-income markets easily, though they are sometimes not enforced.⁸⁸ Generic versions of the same medicines have to overcome a second legal barrier (due to patent protection) governed by customs procedures. Moreover, consumer demand for these generics is likely to be low compared to re-imported branded products.

4.3.2 Access Gaps in High-Income Countries

Another potential concern pharmaceutical companies may have is the perception that these novel licensing practices only address the access gap abroad while ignoring the significant access gap that exists in the U.S. Indeed, an access gap clearly does exist within the U.S. and equitable access licensing would not provide a domestic solution. Equitable access licensing and similar mechanisms rely on the ability to divide markets into two groups—those with branded-drug exclusivity and those with generic competition. Application of these strategies within the U.S. would necessitate a neat division of poor and rich markets. This is clearly infeasible. For this reason, we suggest that governments are more aptly situated to enact domestic solutions to this problem than universities.

Though licensing provisions are unlikely to provide a solution to the access gap in the U.S., the EAL should not present a public relations liability for the pharmaceuticals industry. Will the public criticize pharmaceutical companies for "worrying about people abroad when there are people suffering right here"? While this is a concern for any differential pricing mechanism, the American public's interest in and concern for global health matters have grown substantially in recent years. Additionally, we believe that the specific mechanism of the EAL, the creation of generic competition, would offer some public relations protection. After all, it would be generics manufacturers, not brand-name companies, selling at low prices. While lower prices for identical branded drugs invite public criticism, generic products do not.

● 5. CONCLUSION ○

Global access to medicines represents a life or death scenario for millions of people worldwide. The problem is, in one sense, attributable to societal ingenuity. As a result of biomedical innovations that allow treatment and prevention of disease, we are continuously challenged to distribute the product equitably. For other patients, those suffering from neglected diseases, the economic principles underlying our society seem to have failed them entirely.

Yet this is not a time for the global community to concede defeat. Indeed, recent years have brought about numerous reasons for hope. The Bill and Melinda Gates Foundation has invested billions of dollars into its global health mission in the past six years. The Global Fund to fight AIDS, Tuberculosis, and Malaria involves a multilateral commitment targeting three of the world's biggest sources of disease burden. President George W. Bush has reinforced the United States' leadership role through the creation of the President's Emergency Plan for AIDS Relief. The Drugs for Neglected Diseases Initiative oversees both the research and distribution of novel drugs. In May 2006, a Neglected Diseases Research & Development Appeal will be presented to the World Health Assembly, imploring governments to address the fatal disparities in current funding.⁸⁹ While each of these initiatives is associated with its own set of positive and negative attributes, the current climate is ripe for the enactment of new and creative solutions.

As presented in this paper, we envision the University of Pennsylvania playing a significant role in addressing both the access and the research gap. As a leading research institution, Penn can play a catalytic role in reaffirming the notion that universities have an obligation to enhance global welfare. Penn's extensive research endeavors ensure that sufficient innovation will be produced by the University for the policy changes to be meaningful. Lastly, our paper comes at a time when Penn is actively seeking to enhance its worldwide reputation through global engagement. With careful consideration and thoughtful implementation, Penn has an opportunity to live up to its potential as a leader amongst its peer institutions and ensure that its globally relevant discoveries enhance the welfare of those in greatest need.

● 6. REFERENCES ○

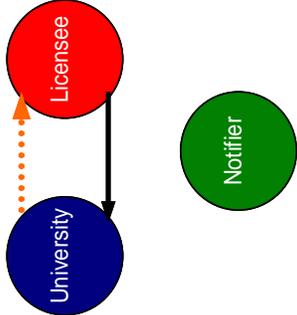
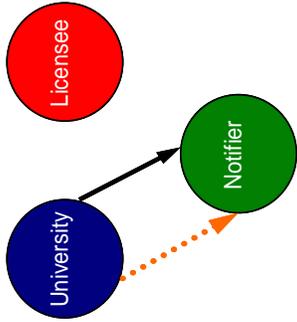
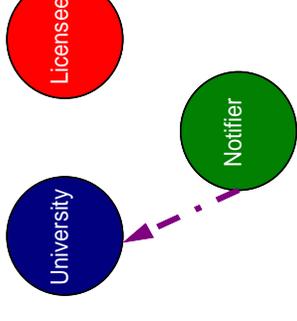
-
- ¹ World Health Organization. Equitable access to essential medicines: a framework for collective action. Geneva: 2004.
 - ² Quick, JD. Essential medicines twenty-five years on: closing the access gap. *Health Policy and Planning* 2003; 18(1): 1-3.
 - ³ World Health Organization. The World Medicines Situation. Geneva: 2004. p. 46.
 - ⁴ Commission on Intellectual Property Rights. Integrating Intellectual Property Rights and Development Policy. London: 2002. p.51. http://www.iprcommission.org/papers/pdfs/final_report/CIPRfullfinal.pdf
 - ⁵ Medecins Sans Frontieres. Surmounting Challenges: Procurement of Anti-Retroviral Medicines in Low- and Middle-Income Countries. Geneva: 2003.
 - ⁶ Pharmaceutical Research and Manufacturers of America. Pharmaceutical Industry Profile 2005 – From Laboratory to Patient: Pathways to Biopharmaceutical Innovation. Washington, DC: 2005.
 - ⁷ Attaran A. How Do Patents and Economic Policies Affect Access to Essential Medicines in Developing Countries? *Health Affairs* 2004; 23: 155-66.
 - ⁸ Outterson K. Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets. *Yale Journal of Health Policy, Law, and Ethics* 2005; V(1): 255-58.
 - ⁹ Boelaert M et al. Letter to the Editor, Do Patents Prevent Access to Drugs for HIV in Developing Countries? *JAMA* 2002; 287: 840.
 - ¹⁰ Fink C and Reichenmiller P. Tightening TRIPS: The Intellectual Property Provisions of Recent US Free Trade Agreements. World Bank Trade Note No. 20. Washington, D.C.: 2005.
 - ¹¹ Drugs for Neglected Diseases Working Group, *Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases*, MSF, September 2001
 - ¹² Trouiller P. 2002. Drug Development for Neglected Diseases, *Lancet*.
 - ¹³ Trouiller P et al. Drug development for neglected diseases: a deficient market and a public-health policy failure. *The Lancet* 2002; 359: 2188-94.
 - ¹⁴ Cohen WM et al. Links and Impacts: The Influence of Public Research on Industrial R&D. *Management Science* 2002; 48(1): 1-23.
 - ¹⁵ Klevorick AK et al. On the Sources and Significance of Interindustry Differences in Technological Opportunities. *Research Policy* 1995; 24(2): 185-205.
 - ¹⁶ Jaffe AB. Real Effects of Academic Research. *American Economic Review* 1989; 79(5): 957-70.
 - ¹⁷ Office of the Vice Provost for Research. <http://www.upenn.edu/research/ResearchStatistics.htm>.
 - ¹⁸ Building on Excellence: The Leadership Agenda. http://www.upenn.edu/provost/strategic_plan.html
 - ¹⁹ <http://www.ctt.upenn.edu/oasis/org/Default.aspx?D=CTT>
 - ²⁰ Humanitarian Licensing Working Group, Science and Intellectual Property in the Public Interest Program, American Academy of Arts and Sciences. <http://sippi.aaas.org/SIPPI%20Humanitarian%20Use%20Report%20-%20July%202004.doc>. Washington, DC: 2005.
 - ²¹ See <http://www.tmgh.org/>
 - ²² Chokshi DA. Universities should foster neglected-disease work. *Nature* (letter) 2005; 435(143).
 - ²³ <http://www.upenn.edu/compact/globally.html>
 - ²⁴ Universities Allied for Essential Medicines. Equitable Access and Neglected Disease License. <http://www.essentialmedicine.org/EAL.pdf>
 - ²⁵ Medecins Sans Frontieres. Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries. Geneva: 2005. <http://www.accessmed-msf.org/documents/untanglingtheweb%207.pdf>.
 - ²⁶ Meldrum J. South African HIV Treatment To Depend on Generic Drugs. *AIDSmap News*. August 7, 2003. <http://www.aidsmap.com/en/news/F5E96962-F1B4-40F2-8969-624-AC8A7D424.asp>.
 - ²⁷ The World Bank Group, Data and Statistics: Country Groups, at <http://www.worldbank.org/data/countryclass/classgroups.htm>
 - ²⁸ Bill and Melinda Gates Foundation Grand Challenges in Global Health, “Terms & Condition – For Non-Profit Organizations”
 - ²⁹ United Nations Development Programme. Human Development Report. New York: 2001.
 - ³⁰ Shaffer E. and Brenner J. “International trade agreements: hazards to health?” *Int J Health Services* 2004.
 - ³¹ Medecins Sans Frontieres, Campaign for Access to Essential Medicines, ‘Untangling the web of price reductions.’ 8th ed., June 2005. <http://www.accessmed-msf.org/documents/untanglingtheweb%208.pdf>
 - ³² Danzon P. and Towse A. “Differential pricing for pharmaceuticals: reconciling access, R&D and patents.” *Int J Health Care Finance Econ* 2003.

- ³³ This includes end-products intended to treat subsets of disease populations; a drug indicated to treat a particular stage or strain of a disease, or a particular category of patients (e.g., AIDS patients with symptomatic HIV infection and CD4 count below 200/mm³).
- ³⁴ <http://www.ctt.upenn.edu/oasis/org/Default.aspx?D=CTT>
- ³⁵ <http://www.upenn.edu/research/DetailedPolicies.htm#IP>
- ³⁶ Bergman, Barry. "Research patently in the public interest: Socially responsible licensing makes Berkeley a leader in the delivery of promising new therapies to the developing world" UC Berkeley News. Available at <http://www.berkeley.edu/news/berkeleyan/2005/12/02_licensing.shtml>
- ³⁷ Freire, M. "Technology transfer's next frontier: global health as a new bottom line." Industry and Higher Education 2003.
- ³⁸ Widdus R and White K. Combating Diseases Associated with Poverty. Initiative on Public-Private Partnerships in Health. Geneva: 2004.
- ³⁹ <http://www.upenn.edu/researchservices/pdfs/ngoip-guide.pdf>
- ⁴⁰ "Malaria, Science and Social Responsibility," *The Scientist*, Volume 19, Issue 6; March 28 2005.
- ⁴¹ http://www.berkeley.edu/news/media/releases/2004/12/13_gates.shtml
- ⁴² <http://www.oneworldhealth.org/media/details.php?prID=9>
- ⁴³ Sale of end products in high income countries would require the negotiation of additional cross-licenses between the third party ND researcher/distributor and the original licensee.
- ⁴⁴ Senate Joint Economic Committee, The Benefits of Medical Research and the Role of the NIH 27, 2000
- ⁴⁵ AUTM Licensing Survey: FY 2003.
- ⁴⁶ Rai A. and Eisenberg S. "Bayh-Dole Reform and the Progress of Biomedicine." Law & Contemporary Problems 2003.
- ⁴⁷ Michigan State University held IPR. See Eyal Press & Jennifer Washburn, The Kept University, Atlantic Monthly, Mar. 2000, at 39.
- ⁴⁸ Princeton University holds IPR. U.S. Patent No. 5,344,932 (issued September 6, 1994).
- ⁴⁹ University of California at San Diego holds IPR. U.S. Patent No. 4,943,533 (issued July 24, 1990).
- ⁵⁰ Columbia University holds IPR. See <http://www.nih.gov/news/070101wyden.htm>.
- ⁵¹ Yale University holds IPR. U.S. Patent No. 4,978,655 (issued on Dec. 18, 1990).
- ⁵² Emory University holds IPR. See Emory Univ., Office of Tech. Transfer, Product Pipeline 5 (2004), http://www.ott.emory.edu/shared_web/technologies/Emory_Pipeline.pdf.
- ⁵³ University of Minnesota holds IPR. See Univ. of Minnesota, Fact sheet on Glaxo-Wellcome AIDS Discovery Settlement (Oct. 5, 1999), http://www.umn.edu/urelate/newsservice/newsreleases/99_10glaxofacts.html.
- ⁵⁴ Emory University holds IPR. See Emory University press release, <http://www.news.emory.edu/Releases/emtri/>.
- ⁵⁵ Duke University holds IPR. U.S. Patent No. 5,464,933 (issued November 7, 1995); U.S. Patent No. 6,133,418 (issued October 17, 2000)
- ⁵⁶ Columbia University holds IPR. U.S. Patent No. 4,599,353 (issued July 8, 1986)
- ⁵⁷ National Institutes of Health CRISP database
- ⁵⁸ <http://www.ctt.upenn.edu/oasis/org/?d=ctt>
- ⁵⁹ Genentech 2005 Annual Report. Available at <http://www.gene.com/gene/index.jsp>.
- ⁶⁰ Medecins Sans Frontieres. SurmouIncome Countries. Geneva: 2003.
- ⁶¹ Medecins Sans Frontieres. Will the Lifeline of Affordable Medicines for Poor Countries be Cut? MSF Article. February 25, 2005. http://www.msf.org/msfinternational/invoke.cfm?component=article&objectid=892A769B-692B-47E4-B7E1C1C20A510F1E&method=full_html
- ⁶² Petersen, M. Lifting the Curtain on the Real Costs of Making AIDS Drugs. New York Times, April 24, 2001.
- ⁶³ McNeil Jr. DG. Yale Pressed to Help Cut Drug Costs in Africa. New York Times, March 12, 2001.
- ⁶⁴ Bristol-Myers Squibb, Press Release. Bristol-Myers Squibb Announces Accelerated Program To Fight HIV/AIDS in Africa. March 14, 2001. <http://www.prnewswire.co.uk/cgi/news/release?id=64424>.
- ⁶⁵ World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelipublic-health approach. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf. Geneva: 2003.
- ⁶⁶ Medecins Sans Frontieres. http://www.doctorswithoutborders.org/news/hiv-aids/briefing_doc_12-10-2005.cfm
- ⁶⁷ World Health Organization. Brief Meeting Report, Guidelines Development Group. "Antiretroviral drugs for the treatment of HIV infection in adults and adolescents in resource-limited settings." 2005. http://www.who.int/3by5/ARVmeetingreport_June2005.pdf
- ⁶⁸ Strong K. et al. "Preventing chronic diseases: how many lives can we save?" The Lancet 2005.
- ⁶⁹ Ramsey, F.P. 1927. "A Contribution to the Theory of Taxation," *Economic Journal* (37): 47-61.
- ⁷⁰ <http://www.worldbank.org/data/countryclass/classgroups.htm>
- ⁷¹ United Nations Development Programme. Human Development Report. New York: 2004.

-
- ⁷²http://www.prb.org/Template.cfm?Section=PRB&template=/Content/ContentGroups/Datasheets/2005_World_Population_Data_Sheet.htm
- ⁷³ Yach D. et al. "The global burden of chronic diseases: overcoming impediments to prevention and control." *JAMA* 2004.
- ⁷⁴ Office of Intellectual Property and Industry Research Alliances, University of California-Berkeley. Socially Responsible Licensing at UC-Berkeley. <http://ipira.berkeley.edu/docs/sociallyresponsible10-05.pdf>.
- ⁷⁵ Herrling, P. "Experiments in Social Responsibility." *Nature*. 2006. 439(7074):267-8.
- ⁷⁶ \$7B was the total size of the vaccine market in 2002; <http://www.sabin.org/PDF/entiredoc.pdf>
- ⁷⁷ "Lessons learned: New procurement strategies for vaccines" Piers Whitehead, Mercer Management Consulting.
- ⁷⁸ Ibid.
- ⁷⁹ http://hc.wharton.upenn.edu/danzon/PDF%20Files/Vaccine%20Supply%20HA_MAY0519.pdf
- ⁸⁰ <http://www.sabin.org/PDF/entiredoc.pdf>
- ⁸¹ http://gavi.elca-services.com/resources/FS_Progress___Achievements_en_Jan05.pdf
- ⁸² Pharmaceutical Research and Manufacturers of America. Pharmaceutical Industry Profile 2005 – From Laboratory to Patient: Pathways to Biopharmaceutical Innovation. Washington, DC: 2005.
- ⁸³ Gellman, Barton. "A Turning Point that Left Millions Behind: Drug Discounts Benefit Few While Protecting Pharmaceuticals Companies' Profits," *The Washington Post*, 2000.
- ⁸⁴ Andrew Farlow, Oxford University: 'Costs of Monopoly Pricing Under Patent Protection', Presentation at Columbia University.
- ⁸⁵ "HIV Drugs for Africa Diverted to Europe" *Washington Post*, 3 Oct 2002.
- ⁸⁶ Outterson, K. "Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets." *Yale Journal of Health Policy, Law, and Ethics* 2005.
- ⁸⁷ 'Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health', World Trade Organization 2003.
- ⁸⁸ Silker, C. "America's new war on drugs: should the United States legalize prescription drug reimportation?" *Journal of Legislation* 2005.
- ⁸⁹ <http://www.researchappeal.org/index.php>

• 7. APPENDICES ○

7.1 Appendix 1 – Mechanism of the Equitable Access License

Phase 1	Phase 2	Phase 3
 <p>University IP transferred to Licensee in basic transaction</p> <p>Licensee's associated rights transferred to University for open licensing purposes</p>	 <p>Potential supplier notifies the University and Licensee</p> <p>University IP + Licensee's necessary associated rights flow to the Notifier</p>	 <p>Notifier's associated rights flow back to the University</p>
<ul style="list-style-type: none"> • University grants Licensee the rights to a particular innovation; Licensee grants back all associated rights (those that could prevent a third party from producing or delivering an end product) <i>solely for EAL purposes</i> 	<ul style="list-style-type: none"> • Simple notification procedure: a third party notifies both the University and the original Licensee that it intends to make, use, or sell the end product in a LMI market 	<ul style="list-style-type: none"> • Upon notification, the university's licensed rights, including associated rights from the licensee, flow to the Notifier (this is an instantaneous consequence of notification) • Final step licenses any Notifier improvements on the technology back to the University for the sole purpose of sublicensing them under the EAL's terms

7.2 Appendix 2 – Equitable Access License

MODEL PROVISIONS FOR AN EQUITABLE ACCESS LICENSE

Version 1.0¹

1. Definitions

- a. “Licensed Technology” means the rights licensed by the University to the Licensee pursuant to [Main Agreement].
- b. “Associated Licensee Rights” means all rights in data, information, know-how, methods, procedures and processes, including patent and marketing rights, possessed by Licensee during the term of this Agreement that are necessary to make, use, sell, offer to sell, import or export an End Product or to perform Neglected Research, including but not limited to biological, chemical, biochemical, toxicological, pharmacological, metabolic, formulation, clinical, analytical and stability information and data.
- c. “Associated Notifier Rights” means all rights in data, information, know-how, methods, procedures and processes, including patent and marketing rights, possessed by a Notifier during the term of the Open License granted to such Notifier that are necessary to make, use, sell, offer to sell, import or export an End Product or to perform Neglected Research, including but not limited to biological, chemical, biochemical, toxicological, pharmacological, metabolic, formulation, clinical, analytical and stability information and data.
- d. “Eligible Country” means any country classified by the World Bank as “Low-income” or “Middle-income” at the time a Notification is made.
- e. “End Product” means any product whose manufacture or use relies upon or is covered by the Licensed Technology.
- f. “Fair Royalty” means:
 - i. For countries classified by the World Bank as “Low-income” at the time of the sales on which royalties are due, 2% of Notifier’s Net Sales of End Products in the Notified Country of Net Sales;
 - ii. For countries classified by the World Bank as “Middle-income” at the time of the sales on which royalties are due, 5% of Notifier’s the Net Sales of the End Products by the Notifier in the Notified Country in question.
- g. “Licensed Technology” means the rights licensed by University to the Licensee pursuant to [Main Agreement].
- h. “Neglected Disease” means any disease, condition, or affliction that, at the time Notification under Section 3.a. is made, either affects less than 200,000 persons in the United States or for which there is no reasonable expectation that the cost of developing and making available in the United States a treatment, prophylaxis, or device for such disease, condition, or affliction can be recovered from sales in the United States of such treatment, prophylaxis, or device.
- i. “Neglected Research” means any use of the Licensed Technology or Associated Licensee Rights in an effort to develop treatments, prophylaxis, or devices for a Neglected Disease.
- j. “Notification” means a writing that announces the intention of a party to receive an Open License.
- k. “Notification Fee” means:
 - i. For Notification to receive an Open License to supply End Products to an Eligible Country that is classified by the World Bank as “Low-income” at the time of Notification, \$5,000;
 - ii. For Notification to receive an Open License to supply End Products to an Eligible Country that is classified by the World Bank as “Middle-income” at the time of Notification, \$50,000;

¹ This license is the product of an independent working group convened by Universities Allied for Essential Medicines.

- iii. For Notification to receive an Open License to perform Neglected Research, \$500.]
 - l. “Notified Country” means an Eligible Country indicated by a Notifier in a Notification.
 - m. “Notifier” means a party that has submitted a Notification to the University and Licensee[along with an appropriate Notification Fee]. [University or Licensee acceptance of the Notification and Notification Fee are not required for a party to be a Notifier or for a Notifier to receive an Open License.]
 - n. “Open License” means a non-exclusive license to the Licensed Technology, Associated Licensee Rights, and Associated Notifier Rights granted by the University to a Notifier from University upon Notification. There are no limitations on the number of Open Licenses that may be received or the parties whom may receive an Open License.
- 2. Licensee Grant: Licensee hereby grants University a license to the Associated Licensee Rights for the sole purpose of granting Open Licenses either to Supply in accordance with Section 3.a. or for Neglected Research in accordance with Section 4.a.. [The licensee also agrees to include, in any patent application for a Licensee Improvement, a sentence reading: “This patent is subject to the provisions of the Equitable Access and Neglected Disease License.”]
- 3. Notification to Supply
 - a. Grant of Open License to Supply: Upon providing to University and Licensee Notification to receive an Open License to supply End Products to an Eligible Country, a Notifier automatically receives an Open License from the University permitting the making, using, selling, offering to sell, importing, and exporting of End Products in the Notified Country and the making and exporting of End Products in any country other than the Notified Country for the sole purpose of supplying End Products to the Notified Country. If Notifier exercises its right to make and export an End Product in any country other than a Notified Country for the sole purpose of export to a Notified Country, then Notifier shall use reasonable efforts to visibly distinguish the End Product it manufactures from the End Product sold distributed by the Licensee in the country of manufacture, but such reasonable efforts do not require Notifier to expend significant expense.
 - b. Fair Royalties: The Open License to supply End Products received by Notifier shall be irrevocable and perpetual so long as Notifier submits to University and Licensee payment of a Fair Royalty on sales of End Products covered by the Licensed Technology or Associated Licensee Rights within 90 days of such sales, such Fair Royalty to be divided equally between University and Licensee. [Failure or refusal of University or Licensee to accept the Fair Royalty shall not terminate or affect in any way the Open License.]
 - c. Notifier Grant: In exchange for receipt of an Open License to Supply, Notifier grants University a license to its Associated Notifier Rights for the sole purpose of granting Open Licenses either to Supply in accordance with Section 3.a. or for Neglected Research in accordance with Section 4.a..
- 4. Notification for Neglected Research
 - a. Grant of Open License for Neglected Research: Upon providing to University and Licensee Notification to receive an Open License to perform Neglected Research, a Notifier automatically receives a worldwide, irrevocable, and perpetual Open License from the University to perform Neglected Research.
 - b. No Royalty: No royalty shall be payable to either the University or the Licensee for the Open License for Neglected Research.
 - c. Notifier Grant: In exchange for receipt of an Open License for Neglected Research, Notifier grants University a license to its Associated Notifier Rights for the sole purpose of granting Open Licenses either to Supply in accordance with Section 3.a. or for Neglected Research in accordance with Section 4.a..

5. Assurance of Freedom to Operate: No license or other transfer of the Licensed Technology or Associated Licensee Rights by the University or Licensee shall be valid unless the terms of this Equitable Access and Neglected Disease License are incorporated therein.
6. Transparency: Notwithstanding any other agreement or provision between the parties, either party may publicize the fact that the Licensed Technology and Associated Licensee Rights are subject to a license that includes this Equitable Access License.

7.3 Appendix 3 – Projected Financial Implications of Equitable Access Licensing

Discounted Cash Flow (DCF) Analysis

DCF values an asset as the projected current and future cash flows related to that asset discounted by some rate back to the present. The discount rate incorporates the opportunity cost of capital (i.e. time value of money) and the premium associated with an investment of comparable risk. The model is attractive for two reasons:

- It is considered the lynchpin of modern valuation.
- It is easy to implement in practice because we are attempting to value a patent, a fixed-life asset, and because free cash flow is simple to calculate in for a royalty (which is simply a cash stream to the license holder).

Valuation Methodology

The losses to the university are a sum of the losses due to a) decreased royalties as a direct result of the licensed product not being sold in LI and LMI countries; and b) the indirect royalties lost due to a decrease in royalty percentages from including the EAL clauses in licensing contracts. The sum of these two values provides the Net Present Value (NPV) of royalties lost to the university, a coherent measure of the impact of EALs on the university's bottom line. The process used is the following:

Calculation of NPV of royalties lost from LI/LMI countries:

1. Multiply the number of products licensed by CTT by the expected revenue per year that a licensed product will generate; this gives the total expected revenue per year from CTT-licensed products.
2. Multiply the result by percentage of CTT-licensed products that are health-related. This removes revenues that are related to licensed technologies which will not be impacted by EALs.
3. Multiply the result by the percentage royalty from license and the percentage of revenue derived from LI and LMI countries. This scales down the revenue to the amount that is impacted by the EAL.
4. Multiply the result by the probability of successful market entry. This is necessary because the majority of licensed products do not ultimately make it to market because of the rigors of the FDA approval process.
5. The result thus far is the cash flow in a given year. However cash flows must be projected for entire useful life of the patent.
6. Lastly, these cash flows must be appropriately discounted back to the present.

Calculation of NPV of royalties lost from decrease in royalty percentage:

1. Same as above, except do not multiply by percentage royalty from license because we are looking at the amount of revenues from the license holder's perspective.
2. We must multiply the overall result by the profit margin of pharmaceutical companies. This assumes that the license issuer (i.e. the university) bears the entire cost of the license holder's expected profit losses in LI and LMI countries.

The sum of these two values is the NPV of royalties lost by the university. A more detailed description of the valuation methodology, assumptions, and sources, has been included in the dynamic model below. Nearly all of the assumptions in the model are extremely conservative. With cooperation from CTT, we will likely see the financial impact of implementing EALs to be even less than the already small amount calculated from the model.

Results

The NPV of royalties lost (based on the assumptions listed in the calculations below) is ~\$576,000, a virtually insignificant amount when compared to the University's annual budget (FY 2005) of \$4.05 billion. Furthermore, this loss will decrease with greater adoption of EALs. Any disincentives for companies to enter

into technology transfer agreements with a university that has adopted an EAL policy will quickly diminish as other universities follow its lead.

Pharmaceutical companies, which are increasingly dependent on universities for their innovation pipeline, will be unable to discriminate against several of the nation's foremost medical research universities acting in concert. Furthermore, one cannot adequately value the University of Pennsylvania's potential for boosting its public image and reputation by leading the academic community towards the adoption of EALs; this alone effectively eliminates the already negligible financial losses it may suffer.

Next Steps

Our goal is to work closely with CTT to develop an even clearer picture of how much the University's bottom line will be impacted by the adoption of EALs. We firmly believe that this number will be even lower than the numbers currently quoted in the conservative assumptions of our model. Additional data we hope to get from CTT and utilize in our analysis include the following:

- Average number of products licensed per year
- Negotiated royalty percentages (historical and by product type)
- Percent of licensed products which ultimately generate royalties
- Average revenues per year from licensed products which make it to market
- Average useful life of patent for licensed products (how many years do they actually generate revenues)

Dynamic Model to Project the Financial Implications of Equitable Access Licensing

Control Panel

Number of products licensed per year	1
Licensing revenue per product per year (in MM) with patent protection ²	\$35.00
Percentage of licensing revenues from health-related technologies	100%
Percentage royalty from licensing	5.00%
Percentage of revenue derived from low-income and lower-middle-income countries	7.00%
Probability of successful market entry ³	16.70%
Useful life of patent ¹	12
Discount rate	4.50%

¹Includes potential recovery time (extensions cannot be filed for utility patents)

²Fixed revenue per year (sales life cycle assumptions not included)

³Completion of pre-clinical studies, clinical trials, NDA review and approval

Source

- (1) CTT(pending); set to 1 to temporarily exclude from model.[‡]
- (2) CTT (pending); temporarily estimated using Assumption 5.[‡]
- (3) CTT (pending); set to 100% to temporarily exclude from model.[‡]
- (4) Thursby, M. and J. Thursby (2002). "University Licensing under Bayh-Dole". 5% is max royalty fee (usually ~2%).[‡]
- (5) Pharm. Research & Mfrs. Of Am., Pharmaceutical Industry Profile 2005—From Laboratory to Patent: Pathways to Biopharmaceutical Innovation 40 (2005). Percentage of revenues from LMI countries: 5-7%.[‡]
- (6) J.A. DiMasi et al. / Journal of Health Economics 22 (2003) 158. Probability from IND to Approval: 16.7%.^{‡†}
- (7) J.A. DiMasi et al. / Journal of Health Economics 22 (2003) 151–185. Mean time for approval: 7.5 years.^{‡†}
- (8) Bloomberg Online: Thirty-year U.S. Treasury Bond as of March 19, 2006. 30-yr Treasury is proxy for risk-free rate.

[‡]Does not include pre-clinical time, time to ramp up production, physician relationship building, distribution etc.

[†]Conservative assumptions (overestimation of inputs); CTT data or more precise sources would likely reduce these numbers

Valuation methodology

1. Cash flow in any given year equals (1)*(2)*(3)*(4)*(5)*(6)
2. Project cash flow for number of years equal to (7)
3. Discount cash flows by (8)

Assumptions

1. Licenses only derive revenue over the patent's useful life
2. Zero revenue if license not exclusive in given country
3. No significant reduction in costs due to fewer patent filings
4. All license structures are based on percentage of revenue and have no additional complexities
5. Temporarily insert revenue which backs out to two times aggregate license income (\$11.9 MM) divided by patent's useful life (overaccounts for upward trend in licensing fees)

Year	0	1	2	3	4	5	6	7	8	9
Cash flow (in MM)	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.020	\$0.020
Year	10	11	12	13	14	15	16	17	18	19
Cash flow (in MM)	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020	\$0.020

NPV of royalties lost from LI/LMI countries (in MM)	\$0.137	(9)
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Additional losses to university*

1. Decrease in negotiated royalty percentages
2. Decrease in number of licenses
3. Decrease in corporate research funding

*Note: these additional losses will likely disappear as a larger number of universities begin to adopt similar licensing policies.

Comments

Can value by assuming university bears loss of profits in developing world countries (see below).
 Unlikely; few technologies likely to go unlicensed due to 5-7% change in value; likely eliminated with concessions in 1.
 Likely small because companies will continue to fund profitable research; difficult to value without implementing licensing policies.

Addition to Control Panel

Profit margin percentage in LI/LMI countries	16%	(10)	Source: Calculated from "How the Fortune 1000 Stack Up In Their Industries." Fortune. April 15, 2002.
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Valuation methodology

1. Expected revenue in LI/LMI country (from licensee's perspective) equals (1)*(2)*(3)*(5)*(6) over (7) years and discounted by (8)
2. Multiply expected revenue by (10) to calculate expected loss due to decrease in royalty percentages

Assumptions

1. University completely bears loss of company profits in developing world countries
2. Profit margins in third-world countries equal profits of Fortune 1000 U.S. Pharmaceutical companies
3. Additional losses to university 2. and 3. are negligible with concessions in royalty percentage
4. No additional recoveries in (9) due to lower royalty percentage

Year	0	1	2	3	4	5	6	7	8	9
Cash flow (in MM)	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.000	\$0.409	\$0.409
Year	10	11	12	13	14	15	16	17	18	19
Cash flow (in MM)	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409	\$0.409

NPV of royalties lost from decrease in royalty percentage (in MM)	\$0.439	(11)
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NPV (total) of royalties lost by university	\$0.576	(9) + (11)
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