Valuation and Licensing in Global Health

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ABSTRACT

Since 1999, two trends have transformed the landscape of treating endemic diseases in the developing world: (1) the establishment of highly effective drug development public private partnerships, which have secured substantial amounts of philanthropic funding to develop new drugs for developing countries and (2) the emergence of tiered pricing for drugs that are under patent protection and that treat diseases in both the developed and the developing world. As a result, the options have increased for both academic institutions and companies for developing new therapies for low- and middle-income countries. This also means that traditional bilateral licensing arrangements will be replaced by multimember networks that bring together the necessary skills for R&D, regulatory work, intellectual property (IP) management, production, and distribution and marketing. New licensing approaches will be needed to ensure that IP issues facilitate, rather than hinder, such collaborations and transactions. This chapter presents evidence that suggests that all parties to such transactions should strive for a no profit–no loss financial model in order to maximize humanitarian benefits.

1. TWO PHARMACEUTICAL INDUSTRIES: TWO PRICING PHILOSOPHIES

In developed countries, the pharmaceutical industry consists of two quite separate and largely nonoverlapping sectors:[1]

- In the *research-driven sector*, new drugs are developed and tested through clinical trials. Typically, a new drug application (NDA) is filed with the FDA; when the NDA is approved, the drugs are sold at legal, patent-protected, monopoly prices based on the benefits the drugs provide to patients.
- In the *generic sector*, drugs that are nearing the end of their patent protection term are prepared for market and, when patents expire, sold competitively at commodity prices based on the cost of production.

According to the Generic Pharmaceutical Association, using IMS health data, generics accounted for 56% of all prescriptions dispensed in the United States in 2005, but less than 13.1% of every dollar spent on prescription drugs. Generics cost, on average, 30% to 80% less than their branded counterparts.[2] Prices for generic drugs are typically 10% to 20% of their prepatent expiration price and are cost based (that is, the price is based on a mark up over the cost of production).[3] Analysis of the financial results of publicly traded generic-drug companies shows that these companies typically operate with a gross margin—the amount by which sales exceed the cost of goods sold—of around 50%.[4] This margin covers the companies' general and administrative costs, marketing and selling costs, and profits.

2. DRUG PRICES IN DEVELOPED COUNTRIES

The United States has had a love–hate relationship with the research-driven sector of the

Stevens AJ 2007. Valuation and Licensing in Global Health. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org.

pharmaceutical industry almost from its inception. Consumers love the new life-saving medications that the industry has been able to discover, but they hate the prices resulting from the patent-protected monopoly.

The issue first emerged in the late 1940s, with the launch of the tetracycline family of antibiotics.[5] This was the first family of antibiotics to be discovered by the U.S. pharmaceutical industry itself. The first antibiotics—penicillin, streptomycin, and neomycin—had been discovered in academic laboratories (penicillin at St. Mary's Hospital in London, U.K. and Oxford University with the critical process scale-up under wartime conditions led by the U.S. Department of Agriculture[6] and streptomycin, and neomycin at Rutgers University[7]). All were licensed non-exclusively and the resulting competition caused prices to fall rapidly.

By contrast, thanks to the patent protection they enjoyed, prices for tetracyclines remained high. However, eventually competition came from overseas. At that time, Italy was the "rogue state" of pharmaceutical patents, and through bids by an Italian company for a U.S. military procurement of tetracyclines, the government became aware of the high profit margins on the patented drugs. This discovery led to hearings focused on the pharmaceutical industry led by U.S. Senator Estes Kefauver, Chairman of the Senate Antitrust and Monopoly Subcommittee, from 1959 to 1963. Kefauver correctly identified that the pharmaceutical industry was making enormous profits on the new generation of antibiotics. Disclosures of price markups of thousands of percents led to sensational headlines across the country and to widespread public outrage. He identified a number of other problems in the industry, notably the lack of any requirement for systematic testing for the safety and efficacy of new drugs and the industry's freedom to advertise new drugs with the flimsiest of scientific support for their claims.

Kefauver drafted a law to increase regulation of the industry. The report included requirements for demonstration of safety and efficacy and for compulsory licensing of patents three years after product launch. His colleague, U.S. Representative Oren Harris, introduced companion legislation in the U.S. House of Representatives, and the combined bill became known as the Kefauver-Harris Amendments to the Antitrust Act. Hearings went on for seven months, in the face of strong opposition from the Pharmaceutical Manufacturers Association and the American Medical Association, and the legislation may well have died were it not for the thalidomide catastrophe, which demonstrated the critical need for a much more rigorous review of new drugs. The Kefauver-Harris Amendment passed, though without the compulsory licensing provision. And while it started the process of FDA reform, no action was taken at that time to control pricing.

The only substantive action the United States has taken to control drug prices has been the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act. This legislation greatly facilitated the development of a vigorous generic drug industry. Companies received an exemption—the Section 271(e) research exemption of the patent laws—allowing them to make and use (but not to sell) a drug during its period of patent protection, for purposes of developing data to prove that a new version of the drug was equivalent to the patented version. The company could then file an Abbreviated New Drug Application (ANDA) with the FDA and be ready to put its generic version of the drug on sale as soon as patents expired. Absent this research exemption, a drug company would enjoy a de facto year or two of additional exclusivity, since generic producers would not be able to make and use the drug for testing until the patent had actually expired.

Despite these legislative changes, drug prices remain a major issue in the United States. The problem was exacerbated when the products of the biotechnology industry were introduced in the mid-1980s. These had substantially higher production costs than those of traditional (small-molecule or simple chemical) drugs, resulting in prices of thousands of dollars per year per patient, an order of magnitude higher

than traditional drugs, already perceived to be high priced. More recently, *orphan drugs* such as Genzyme's Ceredase® for Gaucher's disease and some cancer treatments are even more costly, costing as much as US$300,000 per patient per year.

A combination of third-party payers for the insured and compassionate-access programs for the uninsured has allowed the generally high-priced drug market to persist in the United States. In Canada, Europe, and Japan, however, a combination of single purchaser systems and legislative activities have led to lower prices than those in the United States, although prices for drugs in these countries are still well above the costs of production. The opportunity for American citizens to purchase the same patented drugs in Canada or online at low cost has aggravated the concern of patients over high drug prices in the United States. This has made an impression on the Congress and local government officials.

3. THE DEVELOPING WORLD AND TWO-TIER PRICING

In the developing world, situations have varied widely. Countries such as India, Argentina, and Brazil encouraged the development of the generic-drug industry by recognizing only pharmaceutical process patents. Thus, drugs whose composition of matter was patent-protected in the United States and Europe could legally be produced in these countries by a company that could develop a novel production process. However, countries without their own generic-drug industries could afford only to import drugs whose patents had expired and were subject to generic competition.

The second issue for developing countries is that the diseases that afflict them tend to be very different from those that afflict the developed world, although more recently it has become apparent that the "*diseases of the poor are not the only diseases of the poor*."[8] While Western drug companies have set out to discover and develop drugs to treat the diseases of the developed world, through which they are able to earn an attractive return, these companies have, for the most part, ignored tropical diseases. One study showed that of the 1,339 new drugs introduced between 1975 and 1999, only 13 addressed tropical diseases, and only three addressed tuberculosis, which still takes an enormous human toll in the developing world. A later study identified that even these 13 drugs were poorly suited to the needs of the developing world.[9]

Fortunately, serendipity has sometimes worked to help the developing world. For instance in the early 1980s, the animal health division of Merck (now Merial, Inc.) developed an antiparasitic called ivermectin (Ivomec Plus Cattle Injection®), to treat gastrointestinal roundworms, lungworms, sucking lice, mange mites, cattle grubs, and adult liver flukes in cattle. Ivermectin also had a large market for use in treating lungworm infection in dogs and cats. In addition, the drug was found to effectively treat two human parasitic diseases in sub-Saharan Africa:

- Onchocerciasis, commonly known as river blindness, is a nematode infection transmitted through the bite of black flies. The disease causes intense itching, disfiguring dermatitis, eye lesions, and, over time, blindness.
- Lymphatic filariasis, commonly referred to as elephantiasis, coexists with river blindness in a number of African countries and also occurs in a small number of Latin American countries.

Merck developed ivermectin under the tradename Mectizan® for registration to treat humans for these conditions, but it was the UNICEF-UNDP-World Bank-WHO[10] Special Programme for Research and Training in Tropical Diseases that subsequently conducted the extensive trials needed to establish the safety of mass administered Mectizan® for eradication or control purposes. Merck then created a donation program that has donated enough Mectizan® to treat over 40 million patients a year since 1987.

GlaxoSmithKline (GSK) donates a treatment for parasitic worms, albendazole, which is co-administered with Mectizan®.[11] These

programs have had a major impact on rates of infection for these diseases.

4. AIDS

4.1. *AIDS in the developed world*

The uneasy status quo in the pharmaceutical industry fell apart with the AIDS crisis and the political activism that emerged from it. The crisis created a demand for access to effective, new drugs.

The response to the emergence of HIV/AIDS represents a triumph for basic scientific research in the U.S. and Europe, largely funded by government, and its integration with the pharmaceutical and biotechnology industries. While it now appears that the first person to die of AIDS was an inhabitant of the Democratic Republic of the Congo who died in 1959[12] and that the HIV virus was slowly spreading and infecting people during the 1970s, (a U.S. teen who died in 1969 and a Norwegian sailor who died around 1976 have also subsequently been shown to have been infected with HIV[13]) it was not until 1981 that physicians in San Francisco and New York started noticing an unusual incidence of a rare cancer, Karposi's sarcoma, and of a rare form of pneumonia, *pneumocystis carinii pneumonia*, or PCP, in the gay community. It was only then that it became clear that a new disease was emerging.[14]

Although a new Republican administration took office in early 1981 that was unsympathetic to the gay community, investigators at the U.S. National Institutes of Health (NIH) quickly realized the risk posed by HIV. Scientists at NIH recognized the virus' unique ability to infect and destroy the human immune system. As a result, NIH quickly devoted substantial resources to fighting HIV and, together with the Centers for Disease Control and Prevention (CDC), included funds for investigating its epidemiology in Africa. Progress in fighting the disease was rapid:

- In 1983, Luc Montagnier of the Pasteur Institute in Paris identified a putative infectious agent, which he called lymphadenopathy-associated virus or LAV.
- In 1984, Robert Gallo of the National Cancer Institute in Washington, D.C., confirmed that LAV and a virus he had identified and called human T-cell lymphotropic virus III or HTLV-III were identical and that it was the etiologic agent of AIDS.[15]
- In 1985, a diagnostic test was developed, licensed, and put into routine use for screening blood donations.
- In 1987, Retrovir (AZT), the first drug that was effective against HIV, received FDA approval.
- In 1992, a second antiretroviral drug, Hivid (ddC, discovered by NIH scientists and marketed by Roche), was approved and combination therapy was started.
- In 1996, Invirase (saquinavir; marketed by Roche) the first drug of a second class of drugs, the protease inhibitors, was approved and "triple therapy" was launched.

With triple therapy, HIV infection was transformed from a delayed death sentence, to the extent that opportunistic infections or Kaposi's sarcoma could be treated, into a chronic condition whose victims could enjoy a reasonable quality of life for longer and longer periods as the drug regimen improved. HIV was only the second viral disease for which an effective treatment (as opposed to a prophylactic vaccine) had been discovered, the first having been the use of Acyclovir to treat herpes simplex in 1982.

4.2. *The impact of AIDS on the developing world*

The incidence and impact of AIDS in the developing world, particularly sub-Saharan Africa, dwarfs anything seen in the developed world. In some countries today, a third or more of the adult population is infected with HIV. While prevalence in some Asian countries remains low, the sheer size of the population of India or China means that there are an enormous number of infected people in these countries, official denials notwithstanding.

As AIDS began to be well-controlled in developed countries thanks to highly active antiretroviral therapy (the "triple cocktail" or HAART) in the mid- to late-1990s, the developing world started to demand the same access to these life-

saving medications. But there was a critical difference between AIDS and other diseases. There simply were no older, patent-expired drugs available from generic manufacturers to provide to the developing world. The disease was new, and the drugs to treat it even newer, so the drugs were all still under patent protection and would be for years to come. AZT's patent would be the first to expire, in 2005.

Brazil invoked public-health-crisis measures included in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which allowed it to override international patents and make AIDS drugs in its state-owned pharmaceutical factories and make them available to HIV-infected Brazilians under a free-drug program. Between 1997 and 2002, the cost of treating an AIDS patient in Brazil fell from US$6,500 to US$1,500 per year,[16] and the number of deaths from AIDS was reduced to half.

Conditions in Africa were desperate. There was no capacity to do what Brazil had done, and the cost of importing AIDS drugs at developed-world prices, at an annual per patient cost that was many multiples of average per capita GDP, meant very few people were able to receive treatment. In 2001, 25 million people in Africa were infected with HIV, but only 25,000—just 0.1% of the infected population—were receiving HAART.[17]

In December 1997, the Mandela government passed amendments to the South African Medicines Act to break patents and to allow the manufacture or importation of generic versions. In 1999, the World Health Organization (WHO) raised the issue of patents in the pricing of AIDS medications in developing countries.

In response, six major pharmaceutical companies—Merck, Bristol-Myers, GSK, Pfizer,[18] and Boehringer-Ingelheim—approached WHO in 2000 with an offer to lower prices on AIDS drugs in Africa. The initiative was called Accelerating Access. In return, the companies asked that WHO help distribute the drugs. Discussions began and progressed slowly. Individual companies started various philanthropic initiatives, primarily focused on education, research, and community outreach, but critics were not assuaged and continued to demand lower prices for drugs.

A year after the launch of the initiative, only three countries—Senegal, Uganda, and Rwanda—had reached specific agreements with WHO. Antiretroviral therapy cost US$1,000 to US$1,500 per patient per year through this initiative, which is around 10% of U.S. prices. Then Medecins Sans Frontiéres (MSF) entered the debate. Everything changed in February 2001, when the Indian generics manufacturer Cipla offered to supply MSF with triple cocktail pills for US$350 per patient. Cipla offered to supply African governments with the pills for US$600 per patient per year, US$400 below the Accelerating Access price. Cipla's initiative demonstrated that most pharmaceutical companies only applied for patents in South Africa. Only GSK, Boehringer-Ingelheim, and Agouron tended to apply for patents throughout Africa.

In 2001, 39 pharmaceutical companies filed suit against the South African government to enforce their IP rights and prevent Medecins Sans Frontiéres from buying Cipla's products.

4.3 *Yale University and Zerit*

A pivotal catalyst for change was Amy Kapczynski, a first-year student at Yale Law School in early 2001.

A seemingly innocuous decision made at Yale in 1987—one that most academic institutions would make without hesitation even today without thinking twice about it—backfired and became a major issue in the debate about global health and fair access to medicines. Yale's fateful decision was to allow the licensee of one of their drugs to decide in which countries to apply for patent protection.

The story began in the early 1960s at the Detroit Institute of Cancer Research (now the Barbara Ann Karmanos Cancer Institute), where Jerome Horowitz, working on the then-prevalent theory that cancer was caused by viruses, synthesized a number of compounds that would inhibit DNA replication in the expectation that they would be effective against cancer. Some of the compounds Horowitz synthesized included:

- AZT
- ddC
- ddI
- d4T

The theory was incorrect for the overwhelming majority of types of cancer, so the compounds were not effective and were shelved.

When the HIV epidemic emerged, Horowitz' work resurfaced. Several of his compounds were evaluated against HIV and found to be effective. AZT (Burroughs Wellcome), ddC and ddI (both discovered by the NIH) were all discovered by evaluating the efficacy of Horowitz compounds against HIV

Tai-Shun Lin and William Prusoff of Yale University worked with another Horowitz compound, d4T (stavudine), with funding from NIH and Bristol-Myers Squibb (BMS), to evaluate d4T's effectiveness against HIV. BMS received an exclusive option to exclusive license to any patents that emerged from the work. Prusoff and Lin found d4T to be effective, and Yale filed for a method-of-treating patent on December 17, 1986 (U.S. patent No. 4,978,655 was eventually issued on December 18, 1990). Bristol-Myers Squibb exercised its option and signed a license January 12, 1988. As is normal in academic licenses, Yale gave BMS the right to file in foreign countries, with Yale identified as the assignee, and the company filed corresponding applications in major western countries, such as Europe, Japan, and Canada. Critically, the company decided to include South Africa, Mexico, and Egypt in its filings.

BMS commenced clinical development of stavudine and received FDA approval on June 24, 1994. The product was trademarked Zerit®. In 2001, 13 years after the license had been signed, the South African patent made Zerit too expensive for most South African AIDS patients, particularly those living in the poorest areas (typically the townships). Because South Africa is the commercial gateway to Sub-Saharan Africa, Zerit was similarly unavailable everywhere else on the continent.

Zerit was on the list of essential medicines compiled by Toby Kasper, the head of the Access to Essential Medicines Program for MSF. He had met Amy Kapczynski at an AIDS conference in Durban in July 2000 and immediately realized that Amy could help put pressure on Yale for a better license deal from within.[19] Kapczynski's first recruit to this cause was possibly one of the most embarrassing to Yale—William Prusoff, the inventor of Zerit. Then Kaczynski turned to Michael Merson, Dean of Yale's School of Public Health, who formerly headed the AIDS program of WHO.

On February 14, 2001, MSF wrote to Yale and asked if it "*would consider the importation of generic versions of stavudine for use in providing treatment free of charge to people with HIV/AIDS unable to afford treatment an infringement of your intellectual property rights*," and if not, if Yale would "*issue a voluntary license to allow the importation and use of generic stavudine in South Africa*."

On February 28, 2001: Yale replied, denying the request on legal grounds, because it had granted an exclusive license to BMS. Kapczynski then put reporters at the *Yale Daily News* on the trail of the story. The student paper published its first story on the subject on March 2, 2001, which served to mobilize opinion on campus. A group of students in the graduate student union—which had already been campaigning against Yale's relationship with corporate sponsors—circulated a petition calling on the school to ease its patent. The group collected 600 signatures from students, professors, and researchers on campus. The students also assailed Yale for its close ties with BMS—the company had donated US$250,000 to the school in 1999. Kapczynski carried out legal research on campus and tried, unsuccessfully, to get a copy of the license agreement. She provided the information she discovered to MSF.

On March 9, 2001, MSF responded to Yale suggesting that Yale's own policy stated that a key objective of their technology transfer program was intended to be "*the benefit of society in general*" and pointing out that d4T was not reaching those who needed it in South Africa. Finally, MSF also suggested that Yale had the ultimate power over their patent and could breach their contract with BMS if need be.

Two days later, *The New York Times* ran a story "Yale Pressed to Help Cut Drug Costs in Africa." The impact was almost immediate. On March 14, 2001, BMS issued a statement that

"*The Company will ensure that its patents do not prevent inexpensive HIV/AIDS therapy in Africa. The patent for Zerit, rights to which are owned by Yale University and Bristol-Myers Squibb, will be made available at no cost to treat AIDS in South Africa under an agreement the Company has recently concluded with Yale*." In June 2001 Bristol-Myers signed an "*agreement not to sue*" with Aspen Pharmacare, South Africa's leading generic manufacturer.

So, in less than two years, the world pharmaceutical paradigm had been turned upside down. "Two tier" pricing, whereby drugs could in the future be sold at generic prices in developing countries during the period of patent protected exclusivity had been established. There is some evidence that the pharmaceutical industry, or at least its vaccine sector, has started to accept the concept of tiered or segmented pricing according to ability to pay.[20]

5. THE APPROPRIATE LICENSING APPROACH?

The Yale lesson discussed above shows that every license to a drug or vaccine candidate with the remotest potential for treating developing world needs must include fair-access licensing provisions from the outset. This is because after the license is executed, the university cedes to the licensee control of both the development strategy and the patenting strategy.[21]

The objectives of a licensing program for drugs with the potential to treat developing country diseases should be:

- to maximize the possibilities that the drug will be developed
- to structure the arrangements so that tiered pricing will result, with the poorest countries having access to drugs at the lowest prices

An excellent review of potential licensing approaches and structures was published by the open-access online journal *Innovation Strategy Today* in a special issue jointly published with the American Association for the Advancement of Science.[22] However, the article does not propose any model languages or standard approaches.

Others, however, have put forward such suggestions. With its considerable experience in both developing and licensing neglected disease treatments,[23] the NIH has developed a set of white-knight-model licensing provisions (see Box 1).

A set of provisions has also been developed at Boston University (BU) (see Box 2). They are meant for use as a starting point to discuss products that have markets in both the developed and the developing world. The provisions utilize a nonassert approach to manufacture for sale in developing countries.

If the products envisioned by a partnership would only have relevance in the developing world, then the role of IP protection may only be to provide an incentive for a developing country manufacturer to obtain a license to develop the product, and a second source approach may provide sufficient safeguards. BU's model provisions for these approaches are given in Boxes 2 and 3.

These licensing principles remain valid, even though traditional one-to-one licensing models are not adequate for the complex networks that have evolved over the past five to seven years and have transformed the prospects for effective and affordable therapies for the developing world. The emergence of drug development public-private-partnerships (PPPs), which have secured large amounts of philanthropic funding from the Bill and Melinda Gates Foundation, The Rockefeller Foundation, and so forth, have transformed drug development for neglected diseases:[24]

- Large companies have been motivated to contribute their drug-discovery skills and resources because they are secure in the knowledge that others would be responsible for funding late-stage clinical development.
- Small companies have secured funding to develop technologies with dual-market uses, with the PPPs securing license rights for developing countries at zero or low royalty rates, and the small company retaining rights for use in developed countries.

- Academic institutions have had a new channel to advance their neglected disease discoveries.
- Developing country pharmaceutical companies have found their production and distribution skills in demand.

In addition, the PPPs have had the financial clout to insist on affordability conditions as part of the transactions they have negotiated.

6. LICENSE TERMS FOR DEVELOPING COUNTRY MARKETS

As has been discussed in many forums, it is possible to obtain copies of a substantial number of license agreements from public filings with the Securities and Exchange Commission (SEC).[25] However, only development-stage companies that are publicly traded, or that have filed registration statements to become publicly traded, need to make such filings, and only for material agreements—those affecting 10% of company sales or 5% of company assets.

These restrictions mean that the transactions discussed here are unavailable from SEC sources; the examples that follow are all based on voluntary disclosures. Because the underlying agreements are unavailable and because the examples are based on third-party accounts, these third-party accounts are reported here generally verbatim from the cited sources (sections 6.2 through 6.12 of this chapter).

In the course of researching this article, the author was surprised at the lack of transparency in what was expected to be the most transparent sector of licensing. PPPs, companies, and academic institutions that were approached to discuss transactions they had publicly announced having entered into all expressed an unwillingness to reveal details, even when it was made clear that the information would be used to create a guide for others.

Box 1: National Institutes of Health: Excerpts of White Knight Provisions

Within six (6) months of New Drug Application/Biologic License Application approval in the United States or its equivalent in Europe, Licensee shall send a written report to the Public Health Service detailing the potential Public Sector market to fulfill the public health need for the approved drug or vaccine in Developing Countries, including the impact of any approved competing drug or vaccine. The report shall also include Licensee's proposed amendment to the Commercial Development Plan, Appendix E [not included here], and the Benchmarks and Performance, Appendix D [not included here] to address the needs for Licensed Products in Developing Countries. Licensee will diligently consider if it is possible from a commercial and technical point of view, to satisfy said potential Public Sector market, either directly with Licensee's own resources and/or through joint ventures with third parties. Acceptance of this report and amendment is required by PHS in writing; such acceptance will not be unreasonably denied.

"Public Sector" means the government of a Developing Country, or any entity empowered by the government of a Developing Country to act for said government in matters applicable to this Agreement, organizations within the United Nations system including the World Health Global Organization and UNICEF, and other nonprofit agencies which may purchase drugs or vaccines for delivery, manufacture and/or sale in Developing Countries.

"Developing Country" means countries eligible for support from the Global Fund for Children's Vaccines (GAVI) or successor organization, which at the effective date of this Agreement are those countries with a Gross National Product of less than US$1,000 per capita per year, and at the effective date of this Agreement include the countries listed in Appendix G [not included here].

Source: Stephen Ferguson, NIH, personal communication.

Box 2: Boston University's Nonassert Approach

1. Include in the "WHEREAS" clauses:

WHEREAS, University and Licensee acknowledge that it may serve the public good to make certain drugs available at affordable prices to Non-Market Countries in certain circumstances, with appropriate safeguards to Licensee's economic interests in other markets.

2. Include in the "Definitions":

Market Countries shall mean:

(a) All current and future member countries of the Organisation for Economic Cooperation and Development (OECD), presently consisting of Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States; and

(b) All current and future members of the European Union; and

(c) Russian Federation, Republic of China (Chinese Taipei), Korea, Malaysia and Singapore.

Amend the definition of ***Net Sales*** to exclude sales of products made pursuant to the Non-Suit provision of Section [XX; not given here] from the calculation of Net Sales

Non-Market Countries shall mean all countries other than Market Countries.

Public Sector shall include:

(a) The sovereign government of a country;

(b) Agencies of the United Nations, the World Health Organization, and the World Bank;

(c) Organizations which are members of the International Committee of the Red Cross and Red Crescent;

(d) International charitable agencies (also known as Non-Governmental Organizations or NGOs), including but not limited to Oxfam, Medecins Sans Frontiéres, and so forth;

(e) Organizations substantially supported by philanthropic organizations including but not limited to the Bill and Melinda Gates Foundation, the Rockefeller Foundation, and so forth, specifically including global product development and distribution public-private partnerships.

Trade Dress shall mean the physical appearance of Product as sold in any Market Country by Licensee, including but not limited to such characteristics as shape, color, flavor, tradename, trademark, service mark, etc.

3. Include in the "Grant" clauses:

Non-suit: University and Licensee on behalf of themselves and any successors-in-interest to the Intellectual Property covenant that they will not, before or after the date of this Agreement, assert any claim of infringement (including direct infringement, contributory infringement, and inducing infringement) of the Intellectual Property against any person or entity that sells or offers to sell the Licensed Product to Public Sector entities for use in Non-Market countries, or any entity that manufactures or otherwise makes the Licensed Product for sale to Public Sector entities for use in Non-Market countries, or any person or entity that uses the Licensed Product in a Non-Market country, to the extent such claims relate to or arise out of such manufacture, sale or offer to sell.

Notwithstanding any other provision herein, this non-suit provision shall not apply to Products that bear any element of the Trade Dress used by Licensee in any of the Market Countries, or to Products that have not gained regulatory approval from either the U.S. Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) or been pre-qualified by the World Health Organization pre-qualification scheme.

6.1 *Compulsory licensing models*

Several approaches to establishing fair license terms (and, as will be discussed in Section 6.2 below licensing structures themselves) for developing country markets have looked to compulsory licensing principles for guidance. Such approaches, authorized under the TRIPS Agreement, talk about "adequate remuneration" to the patent holder but without offering specific guidelines.[26] A comprehensive review of the issues of compensation in compulsory licensing has been undertaken by Scherer.[27]

For much of the 1970s and 1980s, Canada had an extensive compulsory pharmaceutical licensing policy. In general, Canada required the recipient of a compulsory license to pay the patent holder a 4% royalty on the *licensee's* sales price. After the Doha Round of WTO, Canada was the first country to implement the TRIPS compulsory licensing principles to supply countries that could not produce drugs for their own use. Canada has continued to use a 4% royalty rate, adjusted for the gross domestic product (GDP) of the country, so that in the poorest countries, a royalty rate of 0.2% would apply.[28, 29]

6.2 *Equitable access license*

Universities Allied for Essential Medicines, which grew out of Amy Kapczynski 's student colleagues (see section 4.3 above), has endorsed an Equitable Access and Neglected Disease License[30] (EAL) created by a working group at Yale. The EAL proposes a US$50,000 fee plus a 5% royalty for licenses to sell in countries defined by the World Bank as "middle-income countries" and a US$5,000 fee and a 2% royalty on sales in the World Bank's "low-income countries. These fees would be split 50:50 with the primary licensee. However, the license terms require the licensee to share with the university all of the know-how necessary to make, use, and sell the licensed products in developing countries, so that the university can, in turn, transfer that know-how to the developing country licensees. The developing country licensees will, likewise, share any know-how they develop with the university. Universities Allied for Essential Medicines formalized this approach as the Philadelphia Consensus Statement at their annual meeting in Philadelphia in October 2006 and provided a mechanism for individuals and organizations to sign on.

The structure the EAL would establish provides the ideal mechanism for providing low-cost drugs to developing countries, but it is a utopian standard that will likely create a strong disincentive to large companies to take out licenses to develop academic technologies. A 1% or 2.5% royalty on sales in developing countries in which the target per patient cost is in cents rather than dollars is unlikely to provide a sufficient incentive for them to provide all of their production know-how to the licensing university. Spinouts are probably equally likely to resist these terms because of their potential to scare away potential downstream partners. In addition, the EAL would put a considerable administrative burden on the university's technology transfer office managing these various flows of confidential know-how. The EAL would therefore likely violate the first of Hippocrates' maxims as applied to academic licensing: First Do No Harm.

As of this writing (February 2007), a significant number of individuals and not-for-profits operating in the global health arena have signed on to the Philadelphia Consensus Statement. Noticeably, no universities have signed on as

Box 3: Boston University Second Source Approach

1. Include in the "Grant" clauses:

Second Source: University may, at any time after the first anniversary of Licensee's receipt of the first regulatory approval to sell Licensed Products, start to qualify a supplier for up to one third of annual requirements of Licensed Products.

corporate entities, and only one person with current, and one person with prior executive authority for academic licensing were listed as initial signatories.

6.3 *Global Alliance for TB Drug Development—Chiron*

In one of the first drug development deals between a drugmaker and a nonprofit organization, the Global Alliance for TB Drug Development announced that it had licensed PA-824, a compound effective against *M. tuberculosis*, from Chiron Corp.[31] PA-824 was discovered and protected by PathoGenesis Inc., which was subsequently acquired by Chiron. Chiron has provided a worldwide exclusive license to the TB Alliance for PA-824 and all its analogs, in return for a modest, one-time licensing fee (modest, that is, compared to the industry average of US$1 million to US$3 million)[32] and yearly threshold R&D investments by the alliance to ensure rapid progress. All preclinical R&D on PA-824 is subcontracted to commercial clinical research organizations (CROs; paid by the TB Alliance), and project management (paid by the NIH) is conducted by the Research Triangle Institute, a not-for-profit that conducts contract research for the NIH and others. If and when development is successful, Chiron has the option of buying back the OECD rights by reimbursing the TB alliance for all development costs. The TB alliance would retain rights in all developing country markets. The deal includes "an expansive commitment" to affordable pricing. The agreement has a grant-back clause that allows Chiron to reenter the TB drug development process, within a specific time period, in wealthy countries. The deal also includes manufacturing options for the company.

Though it has not proceeded beyond the laboratory, the compound, called PA-824, has been shown to be effective against drug-resistant strains of *M. tuberculosis* in tests carried out in vitro. Researchers believe PA-824 may be powerful enough to considerably shorten the current short-course-treatment time of six months, which would enable more people to complete treatment.

6.4 *Institute for OneWorld Health—Celera Genomics*

The Institute for OneWorld Health (iOWH) is a not-for-profit drug company founded by Victoria Hale, a former employee of Genentech and winner of a McArthur Foundation Genius Award in 2006. The company sources drug candidates for the treatment of diseases in developing countries from universities and drug companies and then seeks philanthropic donations to fund clinical development.

In 2002, iOWH licensed Celera Genomics' CRA-3316 as a potential new treatment for Chagas' disease. CRA-3316, formerly known as APC-3116, is a cysteine protease inhibitor. Development has been started in collaboration with NIH.[33] Celera licensed CRA 3316 to iOWH royalty free because, according to Wayne Montgomery, who heads intellectual property at Celera, "*the drug would have gathered dust otherwise*."[34]

6.5 *Institute for OneWorld Health—University of California Berkeley—Amyris Biotechnologies*[35]

In December 2004, the Bill and Melinda Gates Foundation awarded a five-year product development grant to iOWH to create a three-way partnership between iOWH, a university (University of California, Berkeley), and a for-profit company (Amyris Biotechnologies, Inc.). Using synthetic biology, industrial fermentation, and chemical synthesis, the goal of this project is to significantly reduce the cost of artemisinin, a key precursor in the production of artemisinin combination therapies (ACT) for malaria. Artemisinin is chemically converted to one of several derivatives that are then combined with other drugs to make an ACT.

Artemisinin is currently extracted from wormwood plant, which is supplied by farmers in Vietnam and China (and more recently from Africa). Seasonality and availability of the plant contribute to the drug's high price. The project, funded by the Gates foundation, hopes to eliminate the need for plant extraction by utilizing a platform technology of "synthetic biology" developed by Jay Keasling at UC Berkeley. The

goal is to lower the cost of artemisinin-containing drugs ten-fold by producing a consistent, reliable, high-quality supply of artemisinin in microbes.

The US$42.6 million grant was divided among the three parties: US$8 million to UC Berkeley for continued basic research; US$12 million to Amyris for applied research on the fermentation and chemical processes; and US$22.6 million to iOWH to perform the required regulatory work and lead the implementation of the product development strategy for the developing world. UC Berkeley's role focuses on the engineering of drug-precursor-producing microbe. Amyris's efforts span the engineering of the production microbe to optimizing the semi-synthesis of the drug through fermentation and novel downstream synthetic chemistry. The role of iOWHs includes developing a commercialization strategy based on a thorough understanding of worldwide regulatory requirements and an analysis of the current ACT manufacturing supply-chain and distribution models. This one grant enables activities in all three areas of development. It creates an integrated team of partners, each applying its expertise to streamline translation from bench to bedside. The financial terms of the partnership are as follows:

License Grant(s)

- The arrangement is governed by a three-party collaboration agreement and two license agreements (from UC Berkeley to each of Amyris and iOWH).
- UC Berkeley granted iOWH a royalty-free license for the manufacture of artemisinin-based malaria treatments used in the developing world. UC Berkeley further shall grant royalty-free licenses to iOWH for intellectual property developed under the three-party collaboration agreement for use in manufacturing artemisinin-based malaria treatments used in the developing world, and iOWH is to establish partnerships for ACT manufacture and distribution.
- UC Berkeley granted Amyris licenses to develop the manufacturing process for the developing world malaria market. Amyris also has licenses for the developed world malaria market, nonmalaria indications of artemisinin, and alternative uses of the platform worldwide. UC Berkeley further shall grant similar licenses to Amyris for intellectual property developed under the three-part collaboration agreement.
- Amyris shall grant iOWH a royalty-free license for intellectual property developed under the three-part collaboration agreement for the manufacture of artemisinin-based malaria treatments used in the developing world.

Royalties

- The license from UC Berkeley to iOWH is royalty free.
- The license from UC Berkeley to Amyris is royalty free for the developing world malaria market (development for iOWH), and royalty bearing for the developed world and nonmalaria indications in the developing world.

Patents

- Patent costs for UC Berkeley's preexisting patents are shared between iOWH and Amyris.
- UC Berkeley patents on intellectual property arising from the collaborative research may be filed by UC Berkeley and licensed to iOWH and/or Amyris under the prearranged terms mentioned above. Costs are shared by the licensee on a pro rata basis. UC Berkeley has no obligation to file an application if it does not have a commitment by a licensee to pay patent costs.
- Patents that are the sole property of Amyris and/or iOWH may be filed by Amyris and/or iOWH as the case may be, at their own expense.
- Logistics of filing and payment of costs on jointly owned intellectual property will be negotiated in good faith by the joint owners when such joint intellectual property arises. If the joint owners cannot agree, and if iOWH has an ownership interest in a joint property, then iOWH may file and prosecute on behalf of the owners at its own expense.

6.6 *Aeras Global TB Vaccine Foundation—Vanderbilt University*[36]

On May 4, 2006, Aeras and Vanderbilt University announced an exclusive license agreement for a TB vaccine based on technology developed at Vanderbilt. The technology enhances the ability of the Bacille Calmette-Guérin (BCG) vaccine to trigger immune-system responses. Under the agreement, Aeras will use the technology to modify the BCG vaccine and will guide the new vaccine through clinical trials. The license agreement grants Aeras exclusive rights for developing a TB vaccine. If a successful vaccine results from the use of this technology, then Aeras will manufacture the new vaccine at its facility in Rockville, Maryland. Vanderbilt retains rights to the technology as a delivery system for other uses. This could potentially include new vaccines or immunotherapies against other diseases from HIV and malaria to cancer.

The Vanderbilt technology, called proapoptotic BCG, is designed to weaken the BCG bacterium. It is a version of BCG with genetic modifications designed to inhibit the bacterium's ability to stop the programmed cell death of a patient's immune cells. These modifications are likely to result in a vaccine that provides better, longer-lasting protection against TB and may prevent progression to active TB among people with compromised immune systems. The financial terms are as follows:

- Grant: Aeras obtained an exclusive license in its field of use.
- Field of Use: Aeras has an exclusive license to the TB field; Vanderbilt retains rights in other fields.
- Payments/Royalties: The license is royalty bearing (including stacking terms) along with milestone payments.
- Patents: Patent costs paid by Aeras.

6.7 *Global Alliance for TB Drug Development—Bayer Healthcare AG*[37]

Moxifloxacin is an antibiotic first approved in 1999 and currently used in 104 countries to treat certain bacterial respiratory, skin, and intraabdominal infections. It has been used by more than 47 million patients worldwide. Moxifloxacin is generally well tolerated, but treatment may result in certain usually mild side effects, including nausea, diarrhea, and dizziness. In vitro and in vivo studies have demonstrated moxifloxacin activity against *Mycobacterium tuberculosis*. Investigators at Johns Hopkins discovered that substitution of moxifloxacin for isoniazid in the reduced treatment time (two months shorter in mice) of the TB treatment regimen. The treatment regimen included rifampin, pyrazinamide, and either moxifloxacin or isoniazid.

In October 2005, the TB Alliance and Bayer Healthcare AG announced a partnership to coordinate a global clinical development program to study the potential of moxifloxacin to shorten the standard six-month treatment of TB by two to three months. The trials will evaluate whether the substitution of moxifloxacin for one of the standard TB drugs (ethambutol or isoniazid) eliminates TB infection faster than the current standard therapy. If successful and approved by the respective regulatory agencies, a new, shorter regimen could be available in the next five years.

The Phase II/III clinical trial program spans four continents and will enroll close to 2,500 patients with TB. The trials will take place in Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States, and Zambia. If the trials are successful, the partnership aims to register moxifloxacin for a TB indication. Upon regulatory approval, the partnership is committed to making it affordable and accessible in developing countries where TB patients need it most.

For this project, Bayer will donate moxifloxacin for each trial site and will cover the costs of regulatory filings; the TB Alliance will coordinate and help cover the costs of the trials, seeking to leverage support from the U.S. Centers for Disease Control and Prevention (CDC), the Orphan Products Development Center of the U.S. Food and Drug Administration, and the European and Developing Countries Clinical Trials Partnership. In May 2006, the TB Alliance received a US$104 million grant from the Bill and Melinda Gates Foundation. The grant will be used, in part, to fund Phase II and III trials of moxifloxacin with the goal of showing the efficacy of moxifloxacin in reducing TB treatment

times by two months by 2010. The financial terms for this development project are:

- Field of Use: Tuberculosis drugs.
- Payments/Royalties: Products will be made available in developing countries at cost, for use against tuberculosis.
- Patent strategy: Patents previously issued.

6.8 International AIDS Vaccine Initiative—Neutralizing Antibody Consortium

The mission of the International AIDS Vaccine Initiative (IAVI) is to ensure the development of safe, effective, accessible, preventive HIV/AIDS vaccines for use throughout the world. Central to IAVI's mission is to improve access to a vaccine for the developing world,[38] which requires speed of development, as well as availability and affordable pricing. IAVI uses a large portion of its resources to conduct R&D to design, manufacture, and test promising HIV/AIDS vaccine candidates.

In July 2002, IAVI announced the formation of the Neutralizing Antibody Consortium (NAC), a five-year, multimillion dollar research program to develop a preventative HIV/AIDS vaccine that fills a critical gap not addressed by most HIV/AIDS vaccines undergoing clinical trials. The original NAC consisted of four founding institutions. Today, the NAC includes an international group of 15 laboratories, funded by IAVI, representing academia, government, and not-for-profit research organizations. The financial terms for the NAC are:

- IAVI funds individual research work plans for NAC principal scientists; in some cases restricted grant monies are used for selected research projects. These carry special compliance terms that apply specifically to that project.
- IAVI manages intellectual property on behalf of the NAC. IAVI rights include:
  - option for exclusive license to program intellectual property in the field
  - option for nonexclusive license to background intellectual property
- IAVI pays for certain patent costs related to program inventions and background inventions.
- Predetermined sharing of revenues among all collaborators.
- Other provisions include diligence, governance, publications, patent management, and process for adding new members.

6.9 Medicines for Malaria Venture (MMV)—GlaxoSmithKline (GSK)

At the 2003, World Economic Forum's Africa Economic Summit in Durban, South Africa, Medicines for Malaria Venture (MMV) and GSK announced a joint portfolio of projects:

- Fab I—Fatty acid biosynthesis I
- Falcipains—Cysteine protease inhibition
- 4(1H)-pyridones—backups
- PDF—Peptide deformylase inhibitor [terminated in March 2005]

The main objective is to subsidize the socio-economic and public health benefit for the developing world. Any successful medicines discovered as a result of this initiative will be made available in endemic areas on a not-for-profit basis. Research work will take place at the GSK drug discovery unit in Tres Cantos, Spain, which GSK has dedicated to research on diseases of the developing world. The center has a team of 50 permanent staff with particular expertise in drug discovery. The Tres Cantos Center is fully integrated into the GSK R&D organization, which provides expertise and infrastructure for all aspects of drug discovery and development. GSK will contribute funding, staff with drug discovery expertise in malaria, and state-of-the-art facilities. MMV contributes funding for malaria drug discovery projects by subsidizing the employment of additional scientists to join the existing staff at Tres Cantos and expertise from its expert scientific advisory committee (ESAC).

6.10 Harvard University—Medicine in Need

In November 2006, Harvard announced that it would license a new aerosolized tuberculosis vaccine invented by Professor David Edwards to Medicine in Need (MEND), a Cambridge nonprofit founded by the inventor.[39] Sales to developing countries will be royalty free, while sales to developed countries will be royalty bearing,

but Harvard will return a large proportion of the royalties back to MEND. Edward's work was funded by a US$7.6 million grant from the Bill and Melinda Gates Foundation, which stipulated as part of the grant that Harvard would have to license the technology to MEND and that Harvard could not take royalties from MEND's sales to the developing world. The Gates Foundation has also used this strategy in its Grand Challenge Grants.

6.11 *Coley Pharmaceutical Group, Inc.—Gates Foundation*

Coley Pharmaceuticals Group, a publicly traded biotechnology company based in Wellesley, Massachusetts, has agreed to license VaxImmune to the Bill and Melinda Gates Foundation for use in conjunction with a vaccine for postinfection malaria. VaxImmune is a TLR9-agonist designed to enhance both antibody levels and potent killer T-cell immune response to infection or tumors. The agreement is a no-profit/no-loss arrangement, in which all clinical development is performed by the Institute for Tropical Diseases Research, funded by the Gates foundation, while Coley receives no royalties or other payments. Coley has partnered VaxImmune with GSK for cancer and infectious disease vaccines and with Novartis Vaccines and Diagnostics for infectious-disease applications. It will receive royalties on any commercial applications of the technology that emerge from the Gates foundation collaborations.[40]

6.12 *Unattributed transactions*

Various sources[41] quote royalty rates of no more than 3%–5% of sales for those companies that do insist on obtaining a financial return on sales of drugs to the poorest of the poor. Procurement costs for finished products are described as typically being at cost of production or cost of production plus 3%–5%, with agreements having not been reached when a margin of 15% over cost was demanded. However, what was not clear was how overhead, corporate costs, and cost of capital were allocated. At some point, there will need to be some incentive provided if private capital is to be utilized and for-profit entities are to become dependable suppliers, or alternatively the PPPs will need to provide the necessary investments for the construction of dedicated production facilities.

7. CONCLUSIONS: TOWARD APPROPRIATE VALUATION STRUCTURES

The comparisons above clearly show that the right valuation formula is to ask for the licensee(s) in developing countries to take over responsibility for future patent costs and to ask for no upfront fees, no milestone payments, and no running royalties. Any financial return to the university will be derived from opportunities in developed countries. Indeed, if a university's objective truly is to get drugs that have been discovered at rich universities in developed countries, using "other people's money," whether governmental or philanthropic, to the worlds' neediest people as cheaply as possible, then true leadership requires that those same universities not start off the process by putting their hands out and saying, "*We have to charge a royalty*."

Universities are under no obligation, under Bayh-Dole or any other law or regulation, to charge a royalty. The message communicated by asking for a royalty—even the modest rates suggested by the analysis above—would be inappropriate and inconsistent with the public mission of the university. Doing so would cost the moral high ground and weaken universities' ability to lead in this humanitarian endeavor.

Clearly, internal consensus between the research community, academic leadership, and technology transfer offices within the university is needed. The researchers who put their time and effort into developing a drug or vaccine to treat developing country diseases will certainly be happy with this approach, as Yale's experience with William Prusoff shows. The dean of the school of public health is a suitable avenue to the administration, if one is needed, as Amy Kapczynski also found at Yale. The development and public relations offices should be involved to ensure that the institution's objectives are properly portrayed and that the institution receives the appropriate recognition for its humanitarian efforts.

The technology transfer professional's negotiating skills will be called into play when negotiating for the rights and financial terms for any potential uses of the technology in developed countries and for spinout technologies. If there are none, it should be a simple negotiation, with indemnification provisions likely to be the most contentious issue. ■

ACKNOWLEDGMENTS

The author thanks Gerald Keusch, for critically reviewing the manuscript and making many helpful suggestions, and Robert Eiss, Mary Moran, Mark Rohrbaugh, Sandra Shotwell and Gerry Siuta for helpful suggestions, sources, and comments.

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1 Novartis has decided to participate in both sectors and has recycled the name of one of its predecessor companies, Sandoz, to be the focus for this effort.

2 www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm.

3 The first company to receive ANDA approval for a drug receives six months of coexclusivity after patent expiration with the patent holder. Prices come down fairly rapidly with this first entrant, but typically come down substantially further after six months when other companies can launch their own generic versions of the drug.

4 For example, Mylan, Teva, Watson, and Barr Labs.

5 Pearson M. 1969. *The Million Dollar Bugs*. Hudson Press: New York.

6 Lax E. 2004. *The Mold in Dr. Florey's Coat : The Story of the Penicillin Miracle*. John MacRae Books: New York.

7 Ryan F. 1993. *The Forgotten Plague: How the Battle Against Tuberculosis Was Won—and Lost*. Little, Brown: Boston.

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9 Moran M, AL Ropars, J Guzman, J Diaz and C Garrison. 2005. The New Landscape of Neglected Disease Drug Development. *London School of Economics and The Wellcome Trust*. September 2005. www.thegeorgeinstitute.org/shadomx/apps/fms/fmsdownload.cfm?file_uuid=8103EC91-AA42-C19E-182D-A6F3A789A7DC&siteName=iih.

10 UNICEF being The United Nations Children's Fund, UNDP the United Nations Development Program, and WHO the World Health Organization.

11 www.filariajournal.com/content/5/1/11/abstract.

12 aids.about.com/od/newlydiagnosed/a/hivtimeline.htm.

13 www.avert.org/origins.htm.

14 www.avert.org/his81_86.htm.

15 profiles.nlm.nih.gov/MV/Views/Exhibit/narrative/aids.html.

16 Deshpande R. 2006. AIDS in Brazil. Ricardo Reisen de Pinho. Harvard Business School Case 9-506-062. harvardbusinessonline.hbsp.harvard.edu/b02/en/home/index.jhtml?topicSection=gen.

17 Spar D. 2002. Life, Death, and Property Rights: The Pharmaceutical Industry Faces AIDS in Africa. Nicholas Bartlett. Harvard Business School Case 9-702-049, June 13, 2002, harvardbusinessonline.hbsp.harvard.edu/b02/en/home/index.jhtml?topicSection=gen.

18 Pfizer eventually withdrew.

19 Source: archive.salon.com/news/feature/2001/05/01/aids/print.html.

20 See, for example, Meeting the Challenges of Manufacturing and Delivering Affordable Vaccines. Remarks of Jean Stéphenne, president and general manager, GlaxoSmithKline Biologics, at BioVision 2005, Lyon, France.

21 Indeed, Yale reportedly may be in for more bad press over the successor to d4T. Yale announced in June 2006 that it had licensed ed4T, a new and improved version of d4T, to Tokyo-based Oncolys BioPharma. (www.thecrimson.com/article.aspx?ref=515702). However, according to Universities Allied for Essential Medicines, the license agreement does not contain a provision ensuring that developing world HIV patients will have access to the drug.

22 Brewster AL, AR Chapman and SA Hansen. 2005. Facilitating Humanitarian Access to Pharmaceutical and Agricultural Innovation. *Innovation Strategy Today* 1 (3). www.biodevelopments.org/innovation/ist3.pdf.

23 See, for example, Salicrup LA, RF Harris and ML Rohrbaugh. 2005. Partnerships in Technology Transfer: An Innovative Program to Move Biomedical and Health Technologies from the Laboratory to Worldwide Application. *IP Strategy Today* no. 12. www.biodevelopments.org/ip/ipst12.pdf.

24 For a comprehensive account of the emergence and impact of PPPs, see *supra* note 9.

25 Stevens A. 2003. Sources of Comparable Licensing Terms. In *Technology Transfer Practice Manual,* 2nd Edition. Association of University Technology Managers, Northbrook, Ill.

26 See, for example, Article 31.

27 Scherer FM and J Watal. 2002. *Post-TRIPS Options for Access to Patented Medicines in Developing Countries. Journal of International Economic Law* 5(4):913-939,

drawing on Working Group 4 of the Commission for Macroeconomics and Health of the World Trade Organization, 2001.

28 See *supra* note 25.

29 See also Outterson K. 2005. *Nonrival Access to Pharmaceutical Knowledge*. WHO Commission on Intellectual Property Rights, Innovation, & Public Health. 3 January.

30 www.essentialmedicine.org/EAL.pdf.

31 Verbatim from Fuhrmans V. 2002. A Hard Sale: Chiron and Non-Profit Group Agree on Drug-Development Deal. *Wall Street Journal* 1 February 2002. new.tballiance.org/newscenter/view-innews.php?id=482.

32 See supra note 9.

33 www.asbmb.org/ASBMB/site.nsf/web/88F1B8F34BE6C08885256CA300618731/$FILE/ASBMB+Today0402.pdf.

34 www.forbes.com/2003/09/12/cz_zm_0910oneworld.html.

35 www.tmgh.org/case-studies-treatment-for-malaria.php.

36 www.tmgh.org/case-studies-better-tuberculosis-vaccine.php.

37 www.tmgh.org/case-studies-tuberculosis.php.

38 www.tmgh.org/case-studies-aids-vaccine.php. The members of the NAC are: The Scripps Research Institute, the University of Pennsylvania School of Medicine, Weill Medical College of Cornell University, Dana Farber Cancer Institute, Harvard Medical School, University of Wisconsin, Center d'Immunologie de Marseille, the University of Oxford, University of Minnesota, The Children's Hospital of Philadelphia, Global Vaccines, Inc., Oregon Health & Science University, and the Dale and Betty Bumpers Vaccine Research Center of the National Institute of Allergy and Infectious Diseases.

39 www.thecrimson.com/article.aspx?ref=515702.

40 Arthur Krieg, CTO, Coley Pharmaceutical Group. Personal Communication.

41 See *supra* note 8.