

USING THE DOCTRINE OF INFORMED CONSENT TO IMPROVE HIV VACCINE ACCESS IN THE POST-TRIPS ERA

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INTRODUCTION

Acquired Immune Deficiency Syndrome (“AIDS”) kills more people every year than any other infectious disease. Thirty million people have already died from AIDS,² and over 40 million people are currently infected with the human immunodeficiency virus (“HIV”) that causes AIDS.³ There are 14,000 new infections every day and 600 new infections every hour.⁴ In the year 2003 alone, there were 5 million new infections and over 3 million deaths.⁵

The impact of AIDS is most devastating in developing countries, where 95 percent of new infections continue to occur.⁶ Africa is particularly hard-hit.⁷ In at least sixteen African countries, between more than ten percent of the adult population are HIV positive.⁸ Since the people infected with HIV in Africa are often parents, AIDS is destabilizing the family structure and creating a generation of orphans unable to care for themselves.⁹ Because the people infected with HIV in Africa tend to be breadwinners,

¹ The author would like to thank Professor Marjorie Shultz and Patrick Hunnius for their thoughtful comments and criticism; and Ann Maravilla and Nikhil Shah for their diligent editing.

² International AIDS Vaccine Initiative, *The World Needs an AIDS Vaccine*, at <http://www.iavi.org/need/needs.htm> (last visited on January 12, 2004) [hereinafter *Aids Vaccine Need*].

³ UNAIDS, *AIDS Epidemic Update 2003*, at <http://www.unaids.org> >(last visited on January 12, 2004) [hereinafter *AIDS Epidemic Update*].

⁴ International AIDS Vaccine Initiative, *About the HIV/AIDS Epidemic*, at <http://www.iavi.org/need/aboutepidemic.htm> (last visited on January 12, 2004) [hereinafter *About HIV/AIDS epidemic*].

⁵ *AIDS Epidemic Update*, *supra* note 3.

⁶ *About HIV/AIDS*, *supra* note 4.

⁷ UNAIDS, *UNAIDS Releases Report on Global HIV/AIDS Epidemic*, at http://www.iavi.org/highlights/34/unaids_report.asp (last visited on January 12, 2004) [hereinafter *UNAIDS Releases Report*].

⁸ *Id.*

⁹ *Id.* Over thirteen million orphans have been created by HIV; Statement by Jean-Jacques Bertrand, Chairman of Aventis Pasteur, on the International AIDS Vaccine Initiative’s Blueprint Report on Access, at <http://www.iavi.org/highlights/33/>

the AIDS epidemic continues to diminish hard-won economic gains throughout the continent.¹⁰

Ironically, AIDS is most prevalent in the countries that are least able to afford life-extending treatments. Currently, 95% of people living with AIDS are denied access to crucial medicine because neither they nor their governments can afford to purchase the drugs that they urgently need.¹¹ Although some developing nations have attempted, with varying degrees of success, to gain access to affordable medicine through compulsory licensing,¹² parallel importation,¹³ equity pricing, or international funding, AIDS medications still remain outside the reach of millions of people with HIV.¹⁴ Even if the medicine were available, the complexity of treatment and lack of adequate medical infrastructure would undermine the effectiveness of drug therapy.¹⁵ Moreover, because education has not sufficiently decreased high-risk behavior, new cases of HIV infection are expected to increase

media/oldaventis_statement.htm (last visited on February 20, 2004) [hereinafter Statement by Jean-Jacques Bertrand].

¹⁰ See, e.g., Keith E. Maskus, *Ensuring Access to Essential Medicines: Some Economic Considerations*, 20 WIS. INT'L L.J. 563, 563 (2002) (citing survey showing reduced productivity, labor force, and GDP in South Africa due to AIDS epidemic).

¹¹ UNAIDS, Press Statement, Statement of Dr. Peter Piot, Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), on the signing by President Bush of the Global AIDS Act (May 27, 2003), available at <http://www.unaids.org/en/other/functionalities/ViewDocument.asp> (last visited on June 6, 2003).

¹² Compulsory licensing occurs when a license for generic production is issued without permission from the patent holder. In exchange, the patent holder generally receives a reasonable royalty. The issue of compulsory licensing is discussed at length below.

¹³ Parallel importation occurs when third parties purchase drugs from abroad and import them for sale domestically at prices below those offered by the patent holder. Parallel importation is possible because pharmaceutical companies sell their products at different prices to different countries, in part because certain countries have instituted price controls or are able to negotiate lower prices based upon volume. John A. Harrelson, *TRIPS, Pharmaceutical Patents, and the HIV/AIDS Crisis: Finding the Proper Balance Between Intellectual Property Rights and Compassion*, 7 WID. L. SYMP. J. 175, 192–93 (2001).

¹⁴ *Id.*

¹⁵ *AIDS Vaccine Need*, *supra* note 1.

exponentially. The main hope for curbing the spread of HIV, therefore, lies in the development of an effective vaccine.¹⁶

Pharmaceutical companies, governments, and non-profit organizations throughout the world have spent hundreds of millions of dollars in the effort to develop an HIV vaccine.¹⁷ Over 23 years into the epidemic, scientists remain unable to manufacture an effective vaccine.¹⁸ Nonetheless, efforts to develop a vaccine have increased dramatically in the past two years.¹⁹ Currently, over twenty different vaccine candidates are being tested in developing countries such as Thailand, Kenya, Trinidad, Tobago, Uganda, Botswana, and South Africa.²⁰ These countries present desirable locations for vaccine trials in part because of the prevalence of high-risk, HIV-negative participants. Because scientists cannot intentionally expose trial participants to a lethal virus in order to test the efficacy of a vaccine, scientists must test their vaccines on high-risk participants who are likely to become infected through their own behavior during the course of the trial.

It is a normative bioethical principle, and an assumption underlying this article, that anyone who participates in a pharmaceutical trial should benefit from its results.²¹ Because few expect

¹⁶ Larry Gostin, *Vaccination for AIDS: Legal and Ethical Challenges from the Test Tube, to the Human Subject, Through to the Marketplace*, 2 AIDS & PUB. POL'Y JOURNAL 9 (1987).

¹⁷ See *AIDS Research: The Story So Far* (WGBH television broadcast, Apr. 12, 1994).

¹⁸ *Id.* Most recently VaxGen completed testing of its HIV vaccine, but advanced trials revealed the vaccine to be ineffective. See, e.g., Thomas H. Maugh II & Denise Gellene, *AIDS Vaccine Fails in Trials*, L.A. TIMES, Feb. 25, 2003.

¹⁹ International AIDS Vaccine Initiative, *When will an AIDS vaccine be found?*, at <http://www.iavi.org/science/state.htm> (last visited on June 6, 2003).

²⁰ UNAIDS, *Preventing HIV/AIDS Among Drug Users: Case Studies From Asia*, at http://www.unaids.org/whatsnew/press/eng/VaxGen240203_en.html (last visited on June 6, 2003); *South Africa Approves First AIDS Vaccine Trial*, REUTERS NEWS, June 19, 2003; *HIV Vaccine Trials Set to Start in Botswana, US*, SOUTH AFRICAN PRESS ASS'N, May 15, 2003, available at 2003 WL 16243182.

²¹ Support for this position can be found in numerous international bioethical documents. See, e.g., Council for International Organization of Medical Sciences ("CIOMS"), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 12 available at http://www.cioms.ch/frame_guidelines_nov_2002.htm (last visited on February 18, 2004); World Medical Association Declaration of Helsinki, *Ethical Principles for Medical Research Involving Human Subjects*, available at <http://www.wma.net/e/policy/b3.htm> (last visited on

the vaccines currently being tested to prevent HIV transmission,²² it is unlikely that trial participants will benefit directly from inoculation. Nonetheless, individuals are eager to participate in trials in hope of gaining an effective vaccine for their families, their communities, and their countries.

It is unclear, however, whether trial participation will secure vaccine access for developing countries. Historically, there has been an average twenty-year lag between when a vaccine is available in developed countries ("the North") and when it is available in developing countries ("the South"). Some people within the developing world never gain access to life-saving vaccines because they are simply too expensive.²³

The inability of developing countries to gain sufficient access to anti-retroviral treatments foreshadows the difficulties such countries could face in gaining access to an effective vaccine. Many life-saving drugs currently available in the North are cost-prohibitive in the South. In Africa, for example, less than one percent of people with HIV currently receive any treatment at all.²⁴ Based upon the difficulties developing countries have faced

February 18, 2004) [hereinafter *Ethical Guidelines*]. This principle is discussed at greater length in Section V, *infra*.

²² Scientists continue to test vaccines with little hope of efficacy because they anticipate that such testing will reveal data that will enable them to develop a better vaccine in the future.

²³ Geoff Dyer, *A Rainmaker in Pursuit of a Cure for a Modern Plague*, FIN. TIMES, Dec. 24, 2002, available at 2002 WL 104189215; see also International AIDS Vaccine Initiative, *Expanding Access to Vaccines Now Available for Other Diseases*, at <http://www.iavi.org> (last visited on June 6, 2003) [hereinafter *Expanding Access*]. An example is provided by the hepatitis B vaccine, which was first licensed in industrialized countries in 1981. Currently, only 35-40% of the world's infants receive the vaccine, despite the fact that more than one million people die from hepatitis-B related illness each year. *Id.* The hepatitis B vaccine initially cost \$100 per dose, which was cost-prohibitive for many people who needed it. The lack of availability of the expensive hepatitis B vaccine in Senegal foreshadows the possible lack of accessibility should an HIV vaccine ever be developed.

²⁴ See *AIDS Drugs and the Developing World: The Role of Patents in the Access of Medicines*, 12 FORDHAM INTELL. PROP. MEDIA & ENT. L. J. 683, 716 (2002) [hereinafter *Fordham Roundtable*]. (Arguing that pharmaceuticals should cut prices for developing countries.) See, e.g., Access to Essential Medicine, *What is the Campaign?*, available at <http://www.accessmed-msf.org/campaign/campaign.shtml> (last visited on Apr. 16, 2004); See, Media Statement, Southern African Catholic Bishop's Conference (Jan. 7, 2003), at <http://www.catholic-jhb.org.za/articles/aids.html> (last visited on Apr. 16, 2004) Hunger Strikers demand governments and pharmaceuticals provide cheaper AIDS medicines).

in gaining access to essential medicines, there is little reason to expect that timely access to an effective vaccine unless significant steps are taken in advance.

Some advocates argue that access can be achieved by forcing pharmaceutical companies that test their products in developing countries to provide free or subsidized vaccines there through equity pricing.²⁵ Although this position may be morally persuasive, there currently is no legal basis to compel pharmaceutical companies to provide free or subsidized vaccines. Moreover, such a requirement could deter pharmaceutical companies from attempting to develop an effective vaccine by undermining their financial incentives to do so.

This article takes a different approach. It argues that under the doctrine of informed consent, which is well-established in international, European, and American law, as well as the laws of numerous Southern countries hosting trials, pharmaceutical companies have a legal and ethical obligation to discuss with trial participants what steps, if any, they will take to ensure that host countries gains access to any effective vaccine that results from their participation. Any trial that fails to discuss access in advance violates the doctrine of informed consent and therefore is both unethical and illegal.

This proposal is novel in that it calls for a more expansive interpretation of the existing doctrine of informed consent. Traditionally, informed consent requires a discussion of the physical risks a trial participant may face, and the health benefits he or she may experience. The more expansive view of informed consent suggested by this paper, however, recognizes that access to an effective vaccine is a potential benefit that should be negotiated as a part of the informed consent process.

This approach is also novel in that it suggests that both the individual receiving the vaccine and the country hosting the trial should be viewed as participants from whom scientists must receive informed consent prior to proceeding with trials. Traditionally, the doctrine of informed consent has required that scientists discuss health risks and benefits only with the individual being

²⁵ See, e.g., <http://www.aidseti.org/publications/HIVAfford.htm>; <http://www.accessmed-msf.org/prod/publications.asp?sentid=492001011132&contenttype=PARA&> (arguing for equity pricing).

inoculated. This paper suggests that scientists must discuss all risks and benefits—including access—with representatives of the host country prior to commencing trials. Furthermore, any agreement should constitute an enforceable contract that will help ensure that pharmaceutical companies comply with the contract once a vaccine is developed. Once an agreement is reached regarding access with the host countries, individuals can consider the agreement, along with all other risks and benefits, to determine whether or not they wish to participate.

Although this approach, by itself, will not guarantee universal vaccine access, it will help ensure that trial participants are not unfairly exploited for financial gain by pharmaceutical companies who profit from their participation. It also will force pharmaceutical companies to address the issue of access before host countries and individuals agree to participate in trials. This process will promote the value of autonomy that informed consent aims to maximize. Finally, while this paper focuses upon HIV vaccine development, the expansive interpretation of informed consent would require a discussion of access whenever individuals from the South participate in non-therapeutic trials. The suggested model could be equally relevant to other viruses like SARS or hepatitis vaccine trials.

Part II provides a general background regarding HIV vaccines and the vaccine testing process. Part III describes the factual, political, and legal context in which the issue of access to HIV drugs has arisen. In particular, it explains how recent developments in the field of intellectual property law, as exemplified but not limited to the Agreement on Trade-Related Aspects of Intellectual Property Rights (“TRIPS”), may undermine the ability of developing countries to gain access to life-saving medications and vaccines. Part IV explains how the doctrine of informed consent provides a legal and ethical framework for human experimentation. Part V applies the doctrine of informed consent to assess the risks and benefits that HIV vaccine trial participants may face. Part VI explains how an expansive interpretation of informed consent would require scientists and host countries to negotiate the issue of access prior to commencement of human experimentation. It also would require scientists to discuss with individuals the issue of access prior to securing their

trial participation. This requirement could better ensure vaccine access without deterring its development.

FACTUAL BACKGROUND

HOW VACCINES WORK

Vaccines can be either prophylactic or therapeutic. Prophylactic vaccines aim to prevent people from contracting disease, whereas therapeutic vaccines prevent previously contracted diseases from progressing. This paper is confined to discussing prophylactic vaccines.

Vaccination involves the artificial introduction of an antigen into the body to produce an immune response. A successful inoculation prevents or modifies the development of an infectious disease should the recipient subsequently be exposed to the disease-causing antigen.²⁶

Vaccines prevent or stem the development of disease by two basic approaches. One approach works by stimulating the body to produce antibodies²⁷ that directly attack an invading virus.²⁸ A successful HIV vaccine would enable antibodies to attach to the AIDS virus (HIV) and prevent the virus from entering healthy cells.²⁹ Another approach would not prevent cell infection, but rather, would prime the body to suppress the virus on a long-term basis through cell-mediated immunity.³⁰ A cell-mediated vaccine relies on specialized blood cells to identify, attack, and kill infected cells.³¹ Some scientists believe that a successful vaccine would necessarily utilize both approaches.³²

²⁶ CHRISTINE GRADY, *THE SEARCH FOR AN AIDS VACCINE* 12 (1995).

²⁷ Antibodies are small proteins that target and destroy invading microbes and toxins. David Brown, *Tradition May Lead to AIDS Vaccine*, WASH. POST, Feb. 13, 2003, at <http://www.amas.org/asp/ang/noticia.asp?codi=2384>.

²⁸ Gostin, *supra* note 15, at 10.

²⁹ Clair Wood, *Vaccines No Cure for AIDS*, BANGOR DAILY NEWS, Dec. 3, 1993, at <http://pqasb.pqarchiver.com/bangor/71130944.html?MAC=e677a39429bd4abf71364d3d2>.

³⁰ Brown, *supra* note 27.

³¹ Steve Condor, *Can AIDS Be Beaten?*, INDEPENDENT, Mar. 3, 2003, available at 2003 WL 14683461.

³² *Id.*

There are three types of antibody-based vaccines that could potentially prevent HIV infection, each with its own risks and benefits. The first type of vaccine is called a live-attenuated vaccine, such as the vaccine that inoculates against polio. A live-attenuated vaccine incorporates fragments of the actual virus in order to promote antibody response in the recipient. Because a live attenuated vaccine would be relatively inexpensive to produce, some scientists favor developing this kind of vaccine because people in impoverished countries would better be able to afford inoculation.³³

There are, however, substantial risks associated with live vaccines. First, recipients risk actually contracting the disease through a live-attenuated vaccine.³⁴ Second, because HIV is a retrovirus,³⁵ a live-attenuated vaccine would result in a life-long, latent HIV infection. The presence of this latent infection in the body could enhance the likelihood of developing diseases such as cancer.³⁶ Third, if the individual is later exposed to the virus, a live-attenuated vaccine could combine with and reconstitute the virus into a more potent, infectious form.³⁷ For all these reasons, many scientists are hesitant to test live-attenuated HIV vaccines on humans.³⁸

The second type of vaccine is called a whole-killed viral vaccine. With a whole-killed viral vaccine, the viral agent is killed or chemically weakened, placed in solution, and injected into the recipient. Because the vaccine looks like a “live” virus to the immune system, the killed virus triggers antibody production.³⁹ After inoculation, B-cells and T-cells remain to attack and repel

³³ *AIDS Research*, *supra* note 16, at 6.

³⁴ Susan Scholle Connor, *International Law and AIDS in INTERNATIONAL LAW AND AIDS: INTERNATIONAL RESPONSE, CURRENT ISSUES, AND FUTURE DIRECTIONS*, 35, 48 (Lawrence Gostin & Lane Porter eds.1992).

³⁵ Retroviruses hijack cells in order to reproduce. The retrovirus inserts itself into the host cell's DNA, where a copy resides permanently. Julio Godoy, *Health-France: World-First Success Claimed in HIV Vaccine*, Inter Press Service, Feb. 17, 2003, available at 2003 WL 6914196.

³⁶ *Id.*

³⁷ Jeremy Grushcow, *The Ethics of Subject Selection for Testing Life-Attenuated HIV Vaccines*, 6 U. CHI. L. SCH. ROUNDTABLE 113, 116 (1999).

³⁸ *AIDS Research*, *supra* note 16, at 5.

³⁹ BULLETIN OF EXPERIMENTAL TREATMENT FOR AIDS: BETA REPORT, Mar. 1993, at 3.

any subsequent viral invasion, thereby helping to prevent disease if the recipient is exposed to the virus.⁴⁰

Once again, reliance upon whole-killed viral vaccines poses certain risks. For example, as with a live-attenuated vaccine, the recipient risks contracting the disease itself from a whole-killed viral vaccine. In fact, as many as one out of every several hundred people inoculated could become infected from the vaccine.⁴¹ For this reason, most scientists disfavor utilization of or experimentation with whole-killed HIV vaccines.⁴²

A third type of a vaccine is known as a recombinant or genetically-engineered vaccine. In a recombinant vaccine, genetically engineered parts of the virus are synthesized into a solution, which is injected into the recipient. Because only parts of a synthetic virus are used, the vaccine itself is not infectious. Accordingly, recombinant vaccines are generally considered safer for human use than the other two types of vaccines.

There are, however, other disadvantages associated with recombinant vaccines. For example, antibodies produced by a recombinant vaccine may increase rather than decrease the recipient's susceptibility to the disease.⁴³ As a result, vaccines may enhance the possibility of infection, rather than protect against infection.⁴⁴ Moreover, because recombinant vaccines are genetically engineered, they are very expensive to produce.⁴⁵

PARTICULAR PROBLEMS POSED BY HIV VACCINES

After nearly twenty years of experimentation, scientists have been unable to manufacture an effective AIDS vaccine. The genetic variability of HIV makes vaccine development particularly challenging. Generally, attempts to develop vaccines for viruses

⁴⁰ *Id.*

⁴¹ *Perspectives AIDS Vaccines: a Flickering Light at the Tunnel's End*, MEDICINE AND HEALTH, May 23, 1994 [hereinafter *Perspectives*].

⁴² *Id.* Despite the risks, some scientists are still experimenting with this method of vaccination. See also, Denise Gellene, *California Stakes Are High for VaxGen, AIDS Vaccine*, L.A. TIMES, Feb. 22, 2003, available at 2003 WL 2386925.

⁴³ *Id.*

⁴⁴ *Perspectives*, supra note 41, at 4.

⁴⁵ *Id.*

with dramatic genetic variability have failed.⁴⁶ The HIV retrovirus is particularly problematic because of its phenomenal ability to remain latent and mutate within the infected person's body.⁴⁷ Due to the mutations, the outside coating of the virus constantly changes, so scientists cannot precisely define to what antibodies must attach. In other words, scientists who attempt to develop an HIV vaccine must battle a moving target.⁴⁸

The pronounced mutations have created numerous strains of HIV that have spread throughout the world. Scientists have identified between six and nine distinct vaccine strains ("clades") of HIV thus far.⁴⁹ A vaccine developed against one clade is unlikely to be effective against another.⁵⁰ The development of several vaccines may be necessary to eliminate AIDS globally.⁵¹

Another problem presented by HIV vaccine development is that animal and test-tube experimentation remain inconclusive. Under ideal circumstances, a vaccine is tested thoroughly and successfully on animals before scientists proceed with human experimentation.⁵² Yet, scientists have found that human AIDS cannot be reliably imitated in animals.⁵³ For example, experimentation with HIV vaccines on chimpanzees is inconclusive because chimpanzees do not develop AIDS.⁵⁴ In addition, tests on human subjects are necessary because HIV strains developed and tested in the lab are different than the "wild" strains found in HIV-positive individuals. Scientists have found that vaccines that protect against lab-adapted viral strains are ineffective when

⁴⁶ John Moore & Roy Anderson, *The WHO and Why of HIV Vaccine Trials*, NATURE, Nov. 24, 1994 at 313. Because of the adaptability of the virus, scientists similarly have been unable to find an effective long-term treatment plan that can ultimately preclude AIDS's onset. *AIDS Research*, *supra* note 16, at 2.

⁴⁷ *Id.* at 1-2.

⁴⁸ *Id.*; See also, *Doctors, Activists Praise Bush Attack on AIDS in Africa*, THE COMM. APPEAL, Thursday, January 30, 2003, available at 2003 WL 4714378.

⁴⁹ *Perspectives AIDS Vaccines* *supra* note 41, at 8.

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² Gostin, *Vaccination for AIDS*, *supra* note 15, at 10.

⁵³ Michael D. Lemonick & David Bjerklie, *A Successful Failure: AIDS Vaccine*, TIME MAGAZINE, Mar. 10, 2003, available at 2003 WL 7740015.

⁵⁴ Gostin, *Vaccination for AIDS*, *supra* note 15, at 11.

tested on “field isolates” from the blood of HIV-positive individuals.⁵⁵ Because laboratory tests are indeterminate, human experimentation is an imperative component in any effort to develop an HIV vaccine.

HOW VACCINES ARE TESTED

In the United States, the Food and Drug Administration (“FDA”) requires successful safety and efficacy trials before it will license any new product, drug, or vaccine.⁵⁶ There are four stages to the FDA approval process: pre-clinical testing; investigational new drug testing; new drug application testing; and on occasion, post-market surveillance.⁵⁷ In pre-clinical testing, scientists must demonstrate that a drug is sufficiently safe for human testing. During this stage, most new drugs are tested on animals.⁵⁸ After initial animal tests are conducted, the pharmaceutical company must file an investigational new drug (“IND”) application with the FDA. The IND Application must list all active ingredients in the drug, a summary of previous human experience with the drug, a description of the investigation plan, identification of phases of clinical investigation, a list of possible risks and side effects of the drug, a study protocol, and a summary of pharmacological and toxicological effects of the drug on animal.⁵⁹ This pre-clinical testing phase takes approximately thirty months.⁶⁰

If the FDA approves further testing, the pharmaceutical company may begin investigational new drug testing, involving human subjects. Trials are designed to determine safety and immunogenicity⁶¹ and usually proceed in three phases.⁶² Phase I trials generally last six months and require the participation of 20 to

⁵⁵ Wood, *supra* note 29.

⁵⁶ 21 U.S.C. § 355.

⁵⁷ *Id.*; See also James Thuo Gathii, *Rights, Patents, Markets and the Global AIDS Pandemic*, 14 FLA. J. INT’L. L. 261, 235 (2002).

⁵⁸ GRADY, *supra* note 26, at 24.

⁵⁹ 21 C.F.R. § 312.23(a) (2001).

⁶⁰ Gathii, *supra* note 57, at 335.

⁶¹ Immunogenicity determines whether a vaccine prompts antibody generation to fight antigen infection.

⁶² This process may be truncated under certain conditions, such as when a pharmaceutical is testing a drug for terminally-ill patients when no alternative treatment

80 human volunteers.⁶³ The volunteers are injected with the vaccine to test drug safety. Scientists also monitor tolerance to the drug and determine how the drug should be administered, the proper drug dosage, and how the drug is eliminated by the body.⁶⁴

In Phase II, safety and immunogenicity is tested further by injecting several hundred volunteers with the vaccine. Phase II lasts up to eighteen months.⁶⁵ Phase III trials require 3,000 to 10,000 volunteers and test efficacy. Phase III takes several years to complete to ensure that scientists can thoroughly track the vaccine's progress through follow-up visits.⁶⁶ The FDA may terminate Phase III trials if it determines the drug to be unsafe or ineffective.⁶⁷

Establishing efficacy is a lengthy and expensive task. Because Phase III trials are expensive, time-consuming, and require the participation of thousands of volunteers who may be difficult to recruit and supervise, Phase III trials are rarely pursued unless compelling data indicates the vaccine's probable human efficacy.⁶⁸

If, during Phase III, a drug has shown promising results, a pharmaceutical may submit a New Drug Application to the FDA for approval to market the drug.⁶⁹ The FDA may also require post-marketing surveillance to ensure the drug is truly safe and effective.⁷⁰

HIV TRIALS AND ACCESS IN THE POST-TRIPS WORLD

As described above, Phase III trials require the participation of thousands of HIV-negative, high-risk volunteers. Because scientists cannot intentionally expose trial participants to a lethal

exists. Gathii, *supra* note 57, at 336–37. So far, HIV vaccines have adhered to the three Phase process.

⁶³ *Id.* at 335; 21 C.F.R. § 312.44 (2001).

⁶⁴ *Id.*

⁶⁵ *Id.* at 336.

⁶⁶ *Id.*

⁶⁷ 21 C.F.R. § 312.44 2001; Gathii, *supra* note 57, at 336.

⁶⁸ *Id.*

⁶⁹ Gathii, *supra* note 57, at 336.

⁷⁰ *Id.*

virus in order to test a vaccine, they target high risk individuals to test efficacy. This approach saves both time and money, because the more quickly test subjects are exposed to the virus, the more quickly scientists can determine whether the vaccine works.

To preserve scientific integrity, individuals within high risk populations can only participate in HIV vaccine trials once. If a participant has already been inoculated with one vaccine, he or she cannot later participate in trials of another vaccine, because scientists will not be able to tell which vaccine is providing protection.

For these reasons, scientists have a particular interest in testing HIV vaccines in developing countries, where there are large communities of high-risk, HIV negative volunteers.⁷¹ Testing in developing countries also offers the added benefit of lower trial costs.⁷²

Because developing countries urgently need an effective HIV vaccine, and scientists urgently require the participation of developing countries and their citizens in vaccine trials, the interests of scientists and developing countries seem to converge to support HIV vaccine testing in developing countries. A synergistic relationship would only exist, if developing countries can access a successful vaccine once developed. The sad irony is that developing countries that host vaccine trials may not gain access to the vaccine their participation enables unless sufficient steps are taken in advance to ensure access. Historically, individuals in developing countries have been unable to gain access to life-saving medicines that are available in the developed world because

⁷¹ It is not necessary that trials proceed exclusively within the United States for FDA approval. The FDA may accept foreign clinical data to establish safety and efficacy if the clinical studies were "well-designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community." 21 C.F.R. § 312.20(a) (2001). The FDA also will accept data from foreign drug trials if the host country has entered into a reciprocity agreement with the United States. Gathii, *supra* note 57, at 342–43.

⁷² International law and ethical standards require scientists to adhere to the laws of both their host countries and their countries of origin when conducting human trials abroad. Moreover, the FDA will accept results from foreign trials only if scientists complied with generally acceptable ethical standards. 21 C.F.R. § 312.20(a). Nonetheless, some unscrupulous scientists prefer to test in developing countries because they believe they can avoid ethical and legal requirements enforced at home. An extensive discussion of this problem is outside the scope of this paper.

they are prohibitively expensive for decades after they are marketed in the North.

Given the enormity of the AIDS pandemic, the issue of access is particularly contentious with regard to HIV medications. Many life-saving drugs that are currently available in the developed world are cost-prohibitive for individuals in developing countries. In Africa, less than one percent of people with HIV are receiving any treatment at all. Although there are many reasons why individuals in Africa lack adequate health care, poverty is often the root cause, particularly with regard to AIDS treatments. The average African country has a public health budget of ten dollars per person per year, but the cheapest HIV treatment regimen costs \$350 per year; when the cost of implementation is included, the cost rises to \$1600 per year.⁷³

Recent legal developments, particularly in the realm of intellectual property and trade law, will make access to the most effective medications even less likely. The next section explores the factual, legal, and political context in which the issue of access has recently evolved. In particular, the following section explains how recent developments in intellectual property law, as exemplified but not limited to TRIPS, has complicated the issue of access, creating a political firestorm around the issue of HIV prevention and treatment.

HOW PATENT LAW TRIPS UP ACCESS

Historically, many developing countries did not offer patent protection to pharmaceutical products.⁷⁴ They believed that patent protections would promote the interests of foreign corporations at the expense of low-income people by undermining the availability of generic drugs.⁷⁵ Developing countries that did not offer patent protection were able to produce or purchase generic alternatives to medicine and vaccines when brand-name products were cost-prohibitive.⁷⁶ The promotion of generic alternatives

⁷³ *Fordham Roundtable*, *supra* note 23, at 716.

⁷⁴ David P. Fidler, *Neither Science Nor Shamans: Globalization of Markets and Health in the Developing World*, 7 *IND. J. GLOBAL LEGAL STUD.* 191, 209–10 (1999).

⁷⁵ Harrelson, *supra* note 11, at 179.

⁷⁶ It is clear that generic alternatives are much more affordable. For example, according to a United Nations report, 150 mg of the HIV drug fluconazole costs \$55

concurrently creates competition that forces pharmaceutical companies to reduce the prices of patented drugs.

Thanks to TRIPS, adopted as part of the Uruguay Round of the GATT negotiations in 1994, access to generic alternatives has become much more complicated; for many essential drugs, access is completely denied. The next section provides a basic description of patent law and explains how TRIPS has exacerbated the problem developing countries face in gaining access to life-saving medicines and vaccines. It also explains why compulsory licensing provisions in TRIPS do not sufficiently facilitate access to essential drugs in the South.

A BRIEF PRIMER ON PATENT LAW AND TRIPS

Patents allow owners to exclude others from using, making, offering for sale, selling, or importing their patented material. Patent laws seek to promote public welfare by providing protection to patentable, disclosed matter, thereby encouraging innovation reducing competition and facilitating profitability.

TRIPS establish a base level of intellectual property rights, including patent protection that signatories must provide through domestic legislation.⁷⁷ An attempt to harmonize and strengthen global intellectual property rights, TRIPS was negotiated as part of the Uruguay Round of the GATT negotiations under the auspices of the World Trade Organization (“WTO”). Over one hundred countries signed TRIPS on April 15, 1994.

Under Article 27(1) of TRIPS, patentable material includes all new inventions that have a proper inventive step and are capable of industrial utility – including medications.⁷⁸ Article 70(8) specifically requires members to adopt a procedure for collecting

in India, where it is not under patent protection. The same drug costs \$697 in Malaysia, \$703 in Indonesia, and \$817 in the Philippines, where the drug is under patent protection. Similarly, a month's supply of AZT costs \$48 in India, where it is not afforded patent protection. A month's supply of AZT costs \$239 in the United States. Alan O. Sykes, *TRIPS, Pharmaceuticals, Developing Countries, and the Doha “Solution,”* 3 CHI. J. INT'L L. 47, 47 (2002).

⁷⁷ *Agreement on Trade Related Aspects of Intellectual Property Rights*, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, arts. 27–28, LEGAL INSTRUMENTS RESULTS OF THE URUGUAY ROUND, vol. 31, 33 I.L.M. 81 (1994) [hereinafter TRIPS Agreement]. .

⁷⁸ *Id.* at article 27(1).

pharmaceutical patent drug applications.⁷⁹ Patents are to run for at least twenty years from the date of patent application collection.⁸⁰

To retain membership in the World Trade Organization (“WTO”) and enjoy the accompanying free-trade privileges, members must agree to provide the base-level intellectual property rights outlined in TRIPS.⁸¹ In this way, TRIPS differs from prior treaties governing intellectual property in that it employs enforcement mechanisms and injects trade issues into intellectual property rights. Although the least developed countries were given a grace-period until 2016 to adopt the necessary domestic patent laws,⁸² if signatories do not adhere to TRIPS upon the expiration of this grace period, members such as the United States may threaten trade enforcement sanctions.⁸³ Ultimately, the violation of TRIPS may result in the suspension of WTO privileges.

TRIPS arose in part from political pressure pharmaceutical companies leveraged upon the United States government, which in turn pressured other countries to adopt greater intellectual property protection.⁸⁴ The impetus for TRIPS occurred when pharmaceutical companies grew increasingly concerned that they were losing market share because their intellectual property rights were not being respected in the South.⁸⁵ Pharmaceutical

⁷⁹ *Id.* at article 70(8).

⁸⁰ *Id.* at article 33.

⁸¹ J.M. Spectar, *Patent Necessity: Intellectual Property Dilemmas in the Biotech Domain & Treatment Equity for Developing Countries*, 24 HOUS. J. INT’L L. 227, 235–36 (2002).

⁸² This deadline originally was shorter under TRIPS, but the deadline was expanded under the Doha Declaration, discussed at length below.

⁸³ See, Dispute Settlement Understanding, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 2, LEGAL INSTRUMENTS—RESULTS OF THE URUGUAY ROUND vol. 31, 33 I.L.M. 81 (1994) available at www.wto.org/english/docs_e/legal_e/ursum_e.htm (last visited on Apr. 16, 2004). See, e.g., Peter Drahos & John Braithwaite, *Intellectual Property, Corporate Strategy, Globalisation: TRIPS in Context*, 20 WIS. INT’L L. J. 451 (2002). See also, Mario A. Bagley, *Legal Movements in Intellectual Property: TRIPS, Unilateral Action, Bilateral Agreements, and HIV/AIDS*, 17 EMORY INT’L L. REV. 781 (2003).

⁸⁴ Harrelson, *supra* note 11, at 184.

⁸⁵ See, e.g., Drahos & Braithwaite, *supra* note 83, at 467.

industry representatives claimed that the unauthorized reproduction of patented drugs resulted in an industry loss of approximately \$5 billion per year.⁸⁶ Furthermore, they envisioned ongoing, long-term problems caused by easy gray market access to generic copies of their patented drugs.⁸⁷ In order to protect their markets, American pharmaceutical companies formed the vanguard of a movement toward greater protection and recognition of intellectual property rights abroad.

Developing countries, which in general produce little intellectual property, do not directly benefit from recognizing intellectual property rights.⁸⁸ The protection of intellectual property rights eliminates generic competition, thereby increasing the cost of medicine. Further, to protect intellectual property rights, developing countries must adopt and maintain an intellectual property legal system. This process requires the expenditure of resources that arguably could be better used elsewhere.⁸⁹ On the other hand, developed countries, which are net-sellers and exporters of intellectual property, clearly benefit from TRIPS.⁹⁰ Such apparent inequity begs the question of why developing countries signed TRIPS.

Although many have complained that TRIPS was adopted under duress by developing countries, who were threatened with trade sanctions unless they signed,⁹¹ a more charitable view is that developing countries agreed to offer heightened patent protections required under TRIPS in exchange for trade concessions in the areas of textiles and agriculture.⁹² Some developing countries may have feared that without TRIPS, the United States or the European Union would simply unilaterally engage in trade

⁸⁶ Harrelson, *supra* note 11, at 184.

⁸⁷ Drahos & Braithwaite, *supra* note 83, at 467.

⁸⁸ Spectar, *supra* note 81, at 238.

⁸⁹ *Id.*

⁹⁰ Adebambo Adewopo, *The Global Intellectual Property System and Sub-Saharan Africa: A Prognostic Reflection*, 33 U. TOL. L. REV. 749, 757 (2002).

⁹¹ See, e.g., Drahos and Braithwaite, *supra* note 83.

⁹² Recent events at the WTO conference in Cancun beg the question of whether such concessions will be forthcoming and may even call into doubt the long-term viability of the WTO. It remains to be seen whether and how the disagreements highlighted at Cancun will undermine the effectiveness of TRIPS. See, e.g., Peter M. Gerhart, *Reflections: Beyond Compliance Theory — TRIPS as a Substantive Issue*, 32 CASE W. RES. J. INT'L L. 357, 368–69 (2000).

sanctions and revoke their most favored nation privileges as negotiated in bilateral or regional treaties.

TRIPS's extension of patent rights has tremendously undermined access to live-saving medicines in the developing world. Although patent rights promote innovation and the development of crucial medicines, they also hinder free-market competition and allow pharmaceutical companies to enjoy tremendous profit margins by pricing medicines far over their marginal production costs.⁹³ Due to TRIPS, many HIV positive individuals in developing countries have been priced out of the market for many existing drugs. Furthermore, they will not be able to afford new drugs that are developed.

Nor will they be able to afford an effective HIV vaccine. In fact, it is anticipated that due to price-constraints, it may take ten to fifteen years for an HIV vaccine to become available in the developing world after it is licensed.⁹⁴

Compulsory licensing is the silver lining of TRIPS. Yet, compulsory licensing presents its own set of limitations and problems, which are discussed below.

COMPULSORY LICENSING: THE ROAD NOT (YET) TAKEN

TRIPS purports to balance intellectual property rights against recognized public health objectives. However, patent protections undermine public health objectives by enabling pharmaceutical companies to charge higher prices for their products, thereby pricing out of the market many people who desperately need their drugs. In fact, many have argued that patent laws clearly favor the profitability of pharmaceutical companies over the public health needs of individuals who cannot afford patented medicines.⁹⁵

⁹³ As an example, a three-drug cocktail produced by the Indian generic manufacturer Cipla costs 67 cents per day. In the United State, on-patent versions of the drugs costs \$10,000 per year. Trials for these drugs were conducted in South Africa. Now, pharmaceutical companies may market the cocktail at a price of \$730 per year, which far exceeds the Cipla price. See *Fordham Roundtable*, *supra* note 23, at 700–02.

⁹⁴ *Biotechnology, Human Rights, and Intellectual Property*, 96 AM. SOC'Y INT'L L. PROC. 114, 117 (2002) [hereinafter *Biotechnology*].

⁹⁵ Drahos & Braithwaite, *supra* note 83, at 474.

In an attempt to answer such criticisms and accommodate the concerns of developing countries, TRIPS includes provisions that allow compulsory licensing in periods of “national emergency” for domestic use.⁹⁶ Compulsory licensing enables governments to facilitate the availability of generic drugs by granting a license to a local firm for manufacture of a patented product without permission from the patent holder. In exchange, the government is required to pay the patent holder a reasonable royalty.⁹⁷ The granting of compulsory licenses and the remuneration offered are each subject to judicial review by the WTO. TRIPS only permit the issuance of compulsory licenses after attempts to negotiate a license with the patent holder have failed.

Compulsory licensing can reduce the cost of medications by 75 percent by promoting the existence of generic alternatives.⁹⁸ Yet, thus far, developing countries have not relied upon the compulsory licensing provisions with any great degree of success. There are several reasons for this.

First, many developed nations initially interpreted TRIPS to prohibit compulsory licensing for exportation. In other words, a country without production capacity could not license a generic manufacturer abroad to produce a generic alternative for export.⁹⁹ Therefore, any attempts to gain access by compulsory licensing would require the existence of an infrastructure that could produce pharmaceuticals.¹⁰⁰ This interpretation of TRIPS

⁹⁶ TRIPS, *supra* note 77, at art. 31(f).

⁹⁷ *Id.* at art. 31(h). Prior to compulsory licensing, a government must attempt to negotiate a license with the pharmaceutical unless a “national emergency” exists. *Id.* at art. 31(b).

⁹⁸ Harrleson, *supra* note 11, at 190–91.

⁹⁹ Because certain developing countries are exempt from complying with TRIPS until 2005, countries such as India have thus far been able to freely export on-patent drugs to other developing countries. Countries have been able to rely upon generic alternatives produced by countries such as India. *See, e.g.,* James Love, *Access to Medicines: Solving the Export Problem under TRIPS*, available at <http://www.cptech.org/ip/wto/bridges-exports.html>. (last visited June 6, 2003).

¹⁰⁰ *See Conference Report: Implementation of the Doha Declaration on the TRIPS Agreement and Public Health: Technical Assistance – How to Get it Right*, available at www.cptech.org/ip/wto/doha

was hotly contested because the inability of states lacking production capacity to import generic alternatives undermined the effectiveness of the compulsory licensing provisions.¹⁰¹

Over eighty nations met at the 2001 Fourth World Trade Organization (“WTO”) Ministerial Conference in Doha, Qatar in an attempt to resolve the controversy regarding compulsory licensing.¹⁰² Ultimately, the conference resulted in the issuance of the Declaration on the TRIPS Agreement and Public Health (“Doha Declaration”)¹⁰³

The Doha Declaration affirms the right of members to take necessary steps to protect public health.¹⁰⁴ The Declaration further indicates that TRIPS “can and should be interpreted and implemented in a manner supportive of WTO Members’ right to public health, and in particular, to promote access to medicines for all,” and that members have the right “to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.”¹⁰⁵ It also states that each member state “has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS . . . can represent a national emergency or other circumstances of extreme urgency.”¹⁰⁶ The Declaration also reaffirms that each member state “has the freedom to determine the grounds upon which . . . licenses are granted.”¹⁰⁷ A later ministerial interpretation of the Doha Declaration indicates that developing countries

¹⁰¹ After several years of negotiations, on August 30, 2003, members reached a compromise under which an “interim waiver,” subject to ongoing scrutiny and review, would allow certain countries to import drugs produced pursuant to compulsory licenses. *See, e.g.*, Statement on Paragraph 6 of the Doha Declaration, *available at* http://www.wto.org/english/news_e/pres03_e/pr350_e.htm. Despite such progress, it is far from clear that countries will be able to rely on this provision to actually issue licenses, given that Europe and the United States have opposed every attempt to do so, regardless of whether countries had the right to do so under TRIPS.

¹⁰² Susan K. Sell, *TRIPS and the Access to Medicines Campaign*, 20 WIS. INT’L L.J. 481, 518 (2002).

¹⁰³ *See* Doha Declaration, *supra* note 100.

¹⁰⁴ *Id.* at ¶ 4.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at ¶ 5(c).

¹⁰⁷ *Id.* at ¶ 5(b).

may apply for an “interim waiver” permitting exportation of generics produced pursuant to a compulsory license under certain limited circumstances.

The Doha Declaration, however, is not legally binding. Activists and pharmaceutical company representatives have both acknowledged that the Doha Declaration is merely a political statement that does not alter the obligations created by TRIPS.¹⁰⁸ Although ministerial declarations are not legally binding in a WTO dispute, the Doha Declaration does provide persuasive authority regarding whether a nation’s granting of compulsory licenses is permissible under TRIPS.¹⁰⁹

It remains to be seen whether developing nations will successfully issue compulsory licenses for the manufacture of AIDS medications, or if pressure from the North will prevent the South from even attempting to do so. Developing countries that have attempted to license generic production have met fierce legal and diplomatic opposition from the United States and Europe, both of which continue to pressure Southern countries to adopt “TRIPS-Plus” protections.¹¹⁰ In addition, pharmaceutical organizations have filed lawsuits in the past claiming that compulsory licensing violates their constitutional property rights, regardless of whether TRIPS allows compulsory licensing.¹¹¹

¹⁰⁸ Sell, *supra* note 102, at 517–18.

¹⁰⁹ Sykes, *supra* note 76, at 54.

¹¹⁰ 96 ASIL PROC 114, 118 (2002); Ellen’t Hoen, *TRIPS, Pharmaceutical Patents, and Access to Essential Medicines: A Long Way From Seattle to Doha*, 3 CHI. J. INT’L L. 27, 30–31 (2002). The hypocrisy of this position is clearly demonstrated by the anthrax scare in 2001. Someone shipped anthrax in envelopes though the United States Postal Service, which resulted in several deaths. Anthrax is treated by Cipro, which is manufactured by Bayer, a German pharmaceutical. Title 28 U.S.C. §1498 allows the United States to engage in compulsory licensing for government use. When it appeared that Bayer, the manufacturer of Cipro, would be unable to meet with American demand, the United States government investigated generic alternatives. *Fordham Roundtable*, *supra* note 12 at 706–07. Canada actually issued a compulsory license to augment production. David P. Fidler, *Bioterrorism, Public Health, and International Law*, 3 CHI. J. INT’L L. 7, 21 (2002).

¹¹¹ *Biotechnology*, *supra* note 94, at 118; Hoen, *supra* note 110, at 30–31. For example, in 1998, South Africa adopted an amendment to its Medicines and Related Substances Control Act of 1965 that gave its Minister of Health the power to regulate parallel importation and the importation of generic drugs. Harrelson, *supra* note 11, at 185. In response, the Pharmaceutical Manufacturers Association took the Minister of Health and the South African government to court,

Undoubtedly, the United States will continue to pressure countries to adopt stronger protections than those required by TRIPS and threaten unilateral trade sanctions for non-compliance.¹¹² Whether or not such actions would be legitimate, it could be prohibitively costly for any developing country to waste resources on an extended trade dispute with the United States, or on extensive litigation against pharmaceutical manufacturers. Given this context of uncertainty, a developing country would be

arguing that the amendment deprived them of their constitutional right to property. At the same time, the United States placed South Africa on its watch list pursuant to section 301 of its Trade Act of 1974 and the Generalized System of Preferences under Title V of the Trade Act; such actions serve as precursors to trade sanctions. Harrelson, *supra* note 12, at 185-86. The United States also threatened to withhold aid. Although South Africa was removed from the list in 1999, largely due to political pressure from AIDS activists, the United States government continued to monitor South Africa's adherence to TRIPS. President Clinton subsequently issued an executive order stating that he would not undertake actions that would hinder access to HIV medicines in sub-Saharan Africa. He also paradoxically stated that this position would not undermine the intellectual property rights of pharmaceuticals. The United States subsequently granted sub-Saharan Africa funds with which to purchase patented drugs, no doubt in an attempt to stave off attempts to rely upon compulsory licensing or parallel importation.

The United States also has mounted pressure against Brazil, Thailand, Argentina, and India. For example, the United States government threatened trade sanctions when Thailand planned to manufacture the patented AIDS drug ddI. Again, the United States later withdrew its opposition in response to political protest. Thailand, however, has not granted a compulsory license, despite the fact that it has the infrastructure required to engage in domestic production of generic drugs. Sell, *supra* note 102, at 500-01.

In Brazil, the government offers universal access to anti-retroviral treatment to its citizens. Through extensive public health programs, it has reduced AIDS-related mortality by over 50 percent between 1996 and 1999. Brazil's success is based on its ability to produce locally generic AIDS medicines. Hoen, *supra* note 110, at 32. This generic competition has decreased the price of AIDS medicines by 82 percent. Moreover, Brazilian patent law allows compulsory licensing, and the threat of compulsory licensing has allowed the Brazilian government to negotiate discounted drug prices with manufacturers.

Eventually, United States opposition caught up with Brazil. In February 2001, the United States took action against Brazil at the WTO Dispute Settlement Body. Again, the United States withdrew its action due to political pressure. *Id.* It remains unclear whether Brazil will continue to manufacture generic AIDS medicines when the deadline for TRIPS compliance arrives. There is no doubt, however, that any country engaging in compulsory licensing will face ongoing scrutiny from the pharmaceutical industry.

¹¹² Harrelson, *supra* note 11, at 188.

hard-pressed to issue a compulsory license and would undoubtedly face expensive litigation as a result.¹¹³ At this time, no country has yet resorted to compulsory licensing.

The failure of any country to resort to compulsory licensing is, in some ways, also a success: while vigorously resisting any measures that would potentially undermine their patent rights, some manufacturers have taken steps to address the problem on their own terms. For example, some pharmaceutical companies have agreed to price concessions, largely in response to political pressure.¹¹⁴ Other companies have donated medicines to treat certain opportunistic infections that may occur with AIDS.¹¹⁵ Still other companies have provided infrastructure assistance.¹¹⁶ Some pharmaceutical companies have even granted limited voluntary licensing rights for the generic manufacturer of certain drugs.¹¹⁷

Because such efforts have arisen mainly after Southern countries threaten to engage in compulsory licensing, the “generous” actions of pharmaceuticals can be interpreted as an attempt to preserve their intellectual property rights and avoid the parade of horrors they anticipate will result from the licensed, generic production of patented drugs.¹¹⁸ Yet, regardless of motives, these measures enable some people to gain access to life-saving drugs.

Long-term sustainability, however, requires continuing reliance upon the good graces of pharmaceutical companies. It is unclear whether, in the absence of specific guarantees, pharmaceutical companies will continue to supply drugs at an affordable cost on a predictable, long-term basis. Moreover, by accepting

¹¹³ Although no compulsory licenses have been issued, Glaxo recently granted a voluntary license to South African for the manufacture of one of its anti-AIDS drugs. Some perceived this as yet another effort to stave off compulsory licensing.

¹¹⁴ Maskus, *supra* note 9, at 564. This generic competition will diminish as soon as developing countries are forced to adopt domestic patent protection under TRIPS.

¹¹⁵ For example, Pfizer has donated free diflucan to South Africa. Diflucan treats yeast infections that thrive due to HIV. See *Fordham Roundtable*, *supra* note 23, at 697.

¹¹⁶ *Id.* at 731.

¹¹⁷ *Id.* at 726.

¹¹⁸ See, e.g., Sell, *supra* note 102, at 508.

price concessions rather than resorting to compulsory licensing, developing countries may paradoxically strengthen the patent system and ensure that medicines are more expensive in the long-term. They also do not benefit from the technology transfer or domestic investment and economic growth that could accompany local production. Instead, developing countries once again find themselves depending upon charity from the North.

THE RISK OF DETERRENCE

Based on the above, it is clear that pharmaceutical companies are producing products that impoverished individuals desperately need. It is also clear that these companies are, for the most part, selling the drugs at cost-prohibitive prices while generating phenomenal profits for themselves.

Although many would welcome a scenario in which pharmaceutical companies were legally required to either license their drugs for generic production or engage in equity-pricing, this calls to mind the old cliché: be careful what you wish for. Such requirements would dramatically reduce the incentive for companies to develop AIDS vaccines or drugs.

Although it is easy to criticize pharmaceutical companies for price-gauging, it is important to remember that pharmaceutical companies exist to maximize shareholder value.¹¹⁹ Pharmaceutical industry representatives claim that it costs approximately \$500 million, on average, to bring a drug to market;¹²⁰ the United States government estimates this figure closer to \$359 million.¹²¹ In particular, vaccines are expensive to produce and create legal and economic exposure through product liability lawsuits. The likelihood of success with regard to any vaccine is very small compared to the possibility of complete failure.

¹¹⁹ The industry at large seems to fulfill this mission very well: the pharmaceutical sector is consistently one of the most profitable sectors of the United States economy, with average returns on equity of 18.4 percent over the past 32 years. Nitya Nanda & Ritu Lodha, *Making Essential Medicines Affordable to the Poor*, 20 WIS. INT'L L.J. 581 (2002).

¹²⁰ *Id.* Some representatives have even estimated this figure to be \$800 million. *Harvey Bale Jnr Drug Firms' Federation*, GUARDIAN, Feb. 18, 2003, available at 2003 WL 13144127.

¹²¹ Harrelson, *supra* note 11, at 184.

If companies were unable to recoup their costs through sufficient profit, there would be little incentive to develop the HIV vaccine that developing countries desperately need. If pharmaceutical companies were forced to give away or license any newly developed AIDS vaccine, the focus would shift to development of “life-style” drugs with huge profit margins in the North. In fact, the lack of profit incentive is a major reason why so few drugs exist to treat illnesses that primarily occur in impoverished nations.

Whether pharmaceutical companies would really reduce profitability by donating products to countries that could not otherwise afford to purchase the vaccine remains to be seen. Given that an AIDS vaccine would benefit both the North and the South, one could argue that pharmaceutical companies could recoup their research and development costs in the North and still provide a low-cost vaccine to the South due to economies of scale. For this reason, it is questionable whether pharmaceuticals would really lose profits by subsidizing drugs in the developing world. Presumably, the reason such efforts are required is that individuals in such countries do not have money to buy the drugs in the first place. In fact, developing countries only account for 10 percent of pharmaceutical profits – Africa accounts for only 1.6 percent.¹²² Licensing generic production or engaging in equity pricing thus would not dramatically undermine pharmaceutical profits due to lost sales in the developing world.¹²³

A greater concern is that subsidized drugs would be exported to the gray market in the United States and result in the loss of pharmaceutical profits. There is little evidence to support such fears. Despite the lack of patent protection in countries such as India and Brazil, generic drugs have not flooded the profit-rich markets of Europe, the United States, or Japan.¹²⁴ Moreover, TRIPS specifies that compulsory licenses must be

¹²² Harrelson, *supra* note 11, at 190.

¹²³ Jonathan Michael Berger, *Tripping Over Patents: AIDS, Access to Treatment and the Manufacturing of Scarcity*, 17 CONN. INT'L. L. 157, 178 (2002). Of course, if non-government organizations or donor governments purchase drugs through aid donations, then pharmaceutical companies can profit from sales to impoverished individuals. This is a controversial aspect to the foreign aid debate that cannot be explored here.

¹²⁴ *Id.*

used predominantly for the domestic market.¹²⁵ Generics produced pursuant to an interim waiver must meet strict packaging requirements that aim to differentiate generics produced for developing markets and prevent them from entering the gray market.

For this reason, concerns about the gray market appear to be unfounded. Nonetheless, such concerns exist, and even if unsubstantiated, they could deter the development of life-saving drugs. The bottom line is that requiring pharmaceutical companies to provide free or subsidized vaccine, or license generic production for developing countries for an indefinite period of time is likely to threaten further vaccine development. In fact, some pharmaceutical companies have already cautioned that if their patent rights are not respected, they will stop introducing any further HIV drugs, including AIDS vaccines.¹²⁶

Moreover, it is unclear if there is a moral reason why pharmaceutical companies should be forced to bear the entire cost of providing their products to the developing world, simply because their product can solve a crisis for which they are not responsible. Certainly, the global community does not demand that farmers give away food to the hungry, or that landowners provide free housing to the homeless, though food and shelter are clearly necessary for survival.

Yet, there may be a valid distinction with regard to pharmaceuticals, because much of the early research and development money comes from public funds, such as those supplied by the NIH.¹²⁷ In the year 2000, the NIH spent \$16 billion on research and development costs, compared to \$24 billion by the

¹²⁵ TRIPS, *supra* note 77, art. 31(f). Exportation of generic drugs produced pursuant to a compulsory license is now allowed under limited circumstances and subject to extensive bureaucratic requirements. For example, generic exporters must adhere to special packaging rules that aim to ensure that the drugs cannot enter the gray market in the North undetected.

¹²⁶ David Benjamin Snyder, *South Africa's Medicines and Related Substances Control Amendment Act: A Spoonful of Sugar or a Bitter Pill To Swallow?*, 18 DICK. J. INT'L L. 175, 197 (1999)

¹²⁷ Berger, *supra* note 123, at 175–76; Sell, *supra* note 102, at 500–01.

pharmaceutical industry.¹²⁸ In addition, the pharmaceutical industry enjoys favorable economic incentives.¹²⁹ Finally, finally, it is undeniable that the pharmaceutical industry is one of the most profitable industries in existence, raising the question of whether companies are over-compensated by a twenty-year monopoly on their intellectual property.¹³⁰

COUNTRIES THAT HOST TRIALS HAVE A HEIGHTENED CLAIM TO ACCESS

An undeniable tension exists between the need to provide the South with access to life-saving vaccines, and the need to encourage further research and development so that an effective AIDS vaccine can be developed. The debate regarding access and compulsory licensing of HIV medications provides some guidance regarding the issues and political pressures that may surround a successful HIV vaccine.

As tragic as it is for any high-risk individual to be priced out of the market for an effective HIV vaccine, the argument in favor of access will be particularly compelling when articulated on behalf of individuals whose countries have hosted the trials that enable the vaccine's development. Individuals who participate in trials do not directly benefit, because the vaccines are not anticipated to provide significant protection at this stage of development. Rather, the key benefit to trial participation is eventual access to a successful vaccine for the participants and the host countries.

Developing nations that host trials should not be forced to beg for donations from pharmaceutical companies that have profited from their efforts. Under basic principles of distributive justice, those taking on the risks of human experimentation should benefit from their participation.¹³¹ The Kantian categorical imperative against using individuals merely as a means to an end requires pharmaceutical companies to ensure that those who bear the burdens of human experimentation will benefit from the

¹²⁸ *Fordham Roundtable*, *supra* note 23, at 749.

¹²⁹ *Id.*

¹³⁰ Berger, *supra* note 123, at 175–76.

¹³¹ ROBERT A. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 20 (2d. ed. 1988).

trials. A basic respect for life and individual rights prevents utilitarianism from justifying experimentation on individuals who have nothing to gain from the experiment.¹³²

The field of bioethics was founded in part on the hope that the international community could prevent unjust experimentation on and exploitation of subjects who have nothing to gain from the research. The exploitative practices suffered by concentration camp victims in Nazi Germany and Tuskegee syphilis victims in the United States provide gruesome, egregious examples of what can go wrong when scientists experiment on individuals who cannot benefit from the trials.

In a reaction to such atrocities and in an effort to promote equity and beneficence, numerous international bioethical documents were drafted to provide that a group should not participate in a trial unless it will benefit from the results. The documents further indicate that the benefits of human trials must be enjoyed by any community that bore the burden of research.¹³³

For example, the Council for International Organizations of Medical Science ("CIOMS") Model International Guidelines for Biomedical Research Involving Human Subjects¹³⁴ indicate that "[g]roups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of

¹³² Cash payments to participants are generally prohibited under national and international law because they are unduly coercive and vitiate voluntary consent. Informed consent aims to prevent participants from going against their own bodily interests due to financial desperation. Although some may find such a prohibition unduly paternalistic, an extensive discussion of this issue is outside the scope of this paper.

¹³³ US Congress, Office of Technology Assessment (OTA), *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues*, OTA-BP-H-163, at 39 (Washington DC: US Gov Printing Office, Sept. 1995).

¹³⁴ See, e.g., CIOMS Model Guideline 12. See also Carol Levine *Placebos and HIV Lessons Learned*, 28 HASTINGS CENTER REPORT, 43-48 (1998) (arguing that placebo trials are often unethical because participants do not benefit from trial); Christine Grady, *Science in the Service of Healing*, 28 Hastings Ctr. Rep., 34-37 (1998); Robert A. Crouch & John D. Arras, *AZT Trials and Tribulations*, 28 Hastings Ctr. Rep., 26-33 (1998) (arguing that distributive justice requires scientists to share products developed through trials with participants); Leonard H Glantz et al., *Research in Developing Countries: Taking "Benefit" Seriously*, 28 Hastings Ctr. Rep., 38-42 (1998) (recognizing limitations of vague language in CIOMS guidelines, but arguing that ethical trials must share developments with participants).

the research will be equitably distributed.” The CIOMS Guidelines further provide that under principles of justice, experimental treatments developed in the South should be made “reasonably available” to participants upon conclusion of the trial. Similarly, the Declaration of Helsinki indicates that justice requires those bearing the risks of research should enjoy the benefits as well.¹³⁵

In addition, in May 2000, UNAIDS issued a guidance document entitled “Ethical Considerations in HIV Preventative Research.”¹³⁶ The document provides that the expected outcome of the proposed research must benefit the population from which research participants are to be drawn, and that any vaccine shown to be safe and effective should be made available to all participants in the trials in which it was tested, as well as to the communities in which the research was carried out.¹³⁷

According to the principles outlined in such documents, a failure to share the benefits as well as the burdens of research would constitute unfair exploitation. However, these documents are insufficient to ensure access for at least two reasons. First, the guidelines are normative, hortatory documents without the force of law and with no mechanism of enforcement. Nor do they create a legal duty for any entity to provide free or subsidized medicines or vaccines. Thus, while the guidelines provide a moral basis for providing access, they cannot ensure it. Second, the principles are vague. As they are drafted in the abstract in order to meet a wide variety of circumstances, they do not necessarily define what constitutes access, or how access should be provided.

Notably, no enforceable international convention exists that requires pharmaceutical companies to provide access. Nor is one likely to be passed in the near future, due to the successful lobbying efforts of the pharmaceutical industry. Moreover, as described above, requiring pharmaceuticals to provide access could deter trials and reduce the likelihood of developing drugs that benefit the developing world.

¹³⁵ This document is discussed at length below.

¹³⁶ UNAIDS, *Ethical Considerations in HIV Preventive Vaccine Research*, at <http://www.unaids.org/publications/documents/vaccines/vaccines/JC072-EthicalCons-E.pdf> (last visited on April 2, 2004).

¹³⁷ *Id.*, Guidance Point No. 2.

Nonetheless, providing access to trial participants and host countries would send a message to the world that people from developing countries are not just guinea pigs for the pharmaceutical companies, whose bodies may be used without any benefit. Likewise, ensuring that poor people gain access to a vaccine once it is developed comports with principles of distributive justice and sends a message regarding the value of human life: lives are worth saving regardless of the ability to pay for a vaccine. This message is important not only for participants, but also for the entire host nation, so that people do not see their countrymen treated as a resource for Northern post-colonial exploitation. Reducing the spread of HIV would better stabilize Africa, Asia, and central Europe; would create opportunities for economic growth; and would facilitate the development of global markets. It also would reduce the global political threat that some have speculated may result from the nihilistic hopelessness caused by the AIDS scourge.

An expansive interpretation of the doctrine of informed consent would require pharmaceutical companies to discuss access prior to proceeding with trials, thereby minimizing exploitation and enhancing the likelihood of access. As described below, the doctrine of informed consent requires scientists to discuss the risks and benefits of participation with each subject prior to engaging inhuman experimentation. Clearly, a perceived benefit of hosting or participating in trials is access to a life-saving vaccine. Therefore, the issue of access must be fully discussed before individuals can truly give informed consent.

Under the expansive interpretation of informed consent suggested by this paper, pharmaceutical companies conducting HIV vaccine trials in developing nations must disclose what efforts they will make to ensure that members of the host country and individual participants gain access to any vaccine that is ultimately developed. This discussion of access would not result in deterrence, because pharmaceutical companies would not be forced to supply vaccine involuntarily. Rather, a discussion of access before the trials commenced would simply allow developing countries, who are able to supply crucial testing populations not available elsewhere, to harness their power in negotiating access prior to participating.

The next section describes how the doctrine of informed consent has developed in American, European, and international law.

THE DOCTRINE OF INFORMED CONSENT

Due to the atrocities that historically have occurred in the context of human experimentation, a plethora of national and international documents have been adopted in an effort to ensure compliance with bioethical norms. One fundamental bioethical norm is the need to obtain voluntary, informed consent. The doctrine of informed consent ensures that those who bear the risks of human experimentation will make the final decisions regarding their own participation.

The doctrine of informed consent requires that scientists tell each potential participant, in terms he or she can understand, why research is being done, what researchers hope to learn, what will be done in the trial and for how long, what risks are involved, what benefits can be expected, and what other medical interventions are available. Once this discussion is concluded, a potential participant must weigh the risks and benefits to determine whether he or she wants to participate and therefore give his or her informed consent. Scientists conducting the trial must receive voluntary, informed, and competent consent from each proposed subject.

Respect for autonomy and self-determination, based on the belief that a person has a right to bodily integrity, is a main principle underlying the informed consent doctrine. To maximize autonomy, each participant must have enough information to make a choice in line with his or her preferences. Any deception perpetuated by the investigator regarding the purpose, risks, or benefits of the experiment would compromise subject autonomy and undermine the subject's self-determination. Such deception

would violate the doctrine of informed consent and result in cognizable psychological and emotional harm to the subject, regardless of whether the subject experienced physical harm from the experiment.¹³⁸

The doctrine of informed consent involves many of the same principles as contract law. For example, informed consent requires capacity, free power of choice, and the absence of fraud, deceit, duress, or any other form of coercion. Each party must have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. On the other hand, informed consent differs from contract law because an individual is free to withdraw consent from trial participation at any point, even after the trial has begun.

Informed consent may be difficult to procure because the physician's "esoteric knowledge, acquired in the course of arduous training and practical experience, cannot be comprehended by patients."¹³⁹ Moreover, lack of medical certainty may impede joint decision-making as required by informed consent. If risks are unknown or unknowable, informed consent may be unachievable.¹⁴⁰ However, obtaining informed consent need not be an empty ritual. Because full patient participation is desirable, conversations must occur about uncertainties so that joint decision-making is possible.¹⁴¹

¹³⁸ Jay Katz, *EXPERIMENTATION WITH HUMAN BEINGS*, 323-24 (1972). An example of such psychological harm is documented in Katz's discussion of the cancer experiments conducted in 1963 at the Jewish Chronic Diseases Hospital in Brooklyn, New York. Terminally-ill patients were injected with cancer cells in order to determine whether they would be able to reject the foreign cells. This experiment was non-therapeutic and unrelated to the diseases for which they were hospitalized. In general, the patients were not told they were being injected with cancer cells. Numerous patients testified that they experienced psychological and emotional harm from the experiments. Although, they did not physically suffer, a review board ultimately held that the experiments were unethical because they violated the doctrine of informed consent, despite the fact that the patients experienced no physical harm. The deception by the physicians regarding the purpose and the nature of the experiment was sufficient to result in cognizable harm. *Id.* at 9-65.

¹³⁹ Jay Katz, *Informed Consent—Must it remain a fairy tale?*, 10 J. CONTEMP. HEALTH L. & POL'Y 69, 74 (1994).

¹⁴⁰ *Id.* at 81.

¹⁴¹ Jay Katz, *THE SILENT WORLD OF DOCTOR AND PATIENT* 205-06 (1984).

INTERNATIONAL LAW

Several international documents provide ethical standards for human experimentation.¹⁴² Some of the most prominent international instruments governing human experimentation include the Nuremberg Code, the Declaration of Helsinki, the WHO/CIOMS guidelines, and the International Covenant on Civil and Political Rights. Each is addressed briefly below.

THE NUREMBERG CODE

The Nuremberg Code is the most authoritative international legal and ethical document governing international research standards.¹⁴³ The Code indicates “voluntary consent of the human subject is absolutely essential.” It also requires that such consent be informed, competent, and free from coercion.¹⁴⁴

Judges developed the Nuremberg Code in the context of a trial for crimes against humanity stemming from the non-consensual, barbaric experimentation that occurred within Nazi concentration camps.¹⁴⁵ Consequently, the Nuremberg Code casts human experimentation as inherently suspect, and many physicians and researchers consider the Nuremberg Code to be overly restrictive.¹⁴⁶ Particularly problematic is the fact that the Nuremberg Code makes no attempt to accommodate clinical research on children or the mentally-impaired, which may be necessary to develop treatments for afflictions uniquely experienced by these groups.¹⁴⁷

¹⁴² Some may query whether informed consent is a Western value that should not be imposed upon other cultures. This question is outside the scope of this paper. Suffice to say that informed consent is also required under the laws of many developing countries hosting trials, such as Uganda, South Africa, and Thailand. It is also required by international law. Furthermore, pharmaceutical companies must comply with their own laws, even when conducting international trials, so the issue is somewhat moot.

¹⁴³ George J. Annas, *The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and Beyond*, 2 HEALTH MATRIX 119, 121 (1992).

¹⁴⁴ Nuremberg Code, 1947, available online at <http://onlineethics.org/reseth/nuremberg.html>.

¹⁴⁵ Annas, *supra* note 143, at 122.

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

THE DECLARATION OF HELSINKI

In response to perceived limitations of the Nuremberg Code, the World Medical Association formulated the Declaration of Helsinki in 1964.¹⁴⁸ The Declaration of Helsinki consists of recommendations designed by physicians, for physicians conducting human experimentation.¹⁴⁹ The Declaration of Helsinki continues to emphasize the need for informed consent but differs from the Nuremberg Code in permitting scientists to act paternalistically on behalf of their subjects.¹⁵⁰ For example, it permits therapeutic experimentation without informed consent if an independent international committee grants a waiver.¹⁵¹

WHO/CIOMS GUIDELINES

As trials involving human experimentation became more international and complex, the World Health Organization (“WHO”) recognized the need to provide guidance for developing countries hosting trials. To this end, in 1982, the WHO and the Council of International Organizations of Medical Sciences (“CIOMS”) jointly developed the Guidelines for Medical Ethics in Biomedical Research (“CIOMS guidelines”) to assist developing countries in maintaining bioethical research standards.¹⁵² These guidelines were revised several times, most recently in 2002, to account for the growing AIDS epidemic.¹⁵³

The CIOMS guidelines serve as a model for states drafting their own, national regulations on human research.¹⁵⁴ They do

¹⁴⁸ *Id.* The Declaration of Helsinki subsequently has been amended several times, most recently in 2002. See INTERNATIONAL ETHICAL GUIDELINES, *supra* note 20.

¹⁴⁹ *Id.*; GRADY, *supra* note 26, at 39.

¹⁵⁰ *Id.*

¹⁵¹ Annas, *supra* note 143, at 122–23.

¹⁵² Available online at http://www.cioms.ch/frame_guidelines_nov_2002.htm (last visited August 1, 2003). The World Health Organization is a multilateral organization that addresses international disparities in health standards and services and aims to advance the international right to health. See Allyn Lise Taylor, *Making the World Health Organization Work: A Legal Framework for Universal Access to the Conditions for Health*, 18 AM.J.L. & MED. 301, 302 (1992).

¹⁵³ See INTERNATIONAL ETHICAL GUIDELINES, *supra* note 20.

¹⁵⁴ Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT’L L. 513, 527 (2002).

not have the force of law, however, and they do not create enforceable obligations, as the CIOMS has no authority to create or enforce law.

The CIOMS guidelines require every investigator to obtain voluntary informed consent from every prospective subject.¹⁵⁵ Yet, the CIOMS guidelines recognize that, although research in developing countries is essential due to the life-threatening diseases that occur there, the ability to obtain informed consent from subjects in developing countries may be undermined by a lack of education.¹⁵⁶ For these reasons, if the community members do not understand the implications of participation sufficiently to give informed consent, an intermediary or trusted leader may assist others in determining whether the objectives and consequences of the study warrant their participation. This accommodation aims to facilitate ethical human experimentation in populations where potential participants may be less capable of articulating or assessing their own preferences.¹⁵⁷

In addition, CIOMS guidelines require scientists to disclose to individual participants “whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects . . . and whether they will be expected to pay for them.”¹⁵⁸ In so providing, the CIOMS guidelines is one of the few documents that explicitly recognizes that access is one of the possible benefits of trial participation that should be discussed as part of the informed consent process.

OTHER INTERNATIONAL CONVENTIONS

The Universal Declaration of Human Rights does not directly address human experimentation. It does, however, indicate that all people have a right to bodily integrity.¹⁵⁹ The International Covenant on Civil and Political Rights is more specific; it dictates, “[n]o one shall be subjected to torture or to

¹⁵⁵ CIOMS Guideline 4.

¹⁵⁶ For an in-depth discussion of how informed consent obtained from individuals in developing countries is often illusory, see Meier, *supra* note 154, at 530–531.

¹⁵⁷ Annas, *supra* note 143, at 125.

¹⁵⁸ CIOMS Guideline 5(12).

¹⁵⁹ G.A. Res. 217, U.N. GAOR, 3d Sess., Supp. No. 51, at 3, U.N. Doc. A/810 (1948).

cruel, inhuman, or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”¹⁶⁰

THE UNITED STATES

A Presidential Commission for the Protection of Human Subjects of Biomedical and Behavioral Research presented the Belmont Report to the United States Senate in 1978.¹⁶¹ The Department of Health and Human Services (“DHHS”) incorporated the Belmont Report into its regulations in 1981, thereby giving the report legal force. These regulations provide mandatory guidelines for all research involving human subjects that is supported or conducted by the federal government.¹⁶² In addition, the Food and Drug Administration (“FDA”) has adopted similar regulations, which govern all experimentation for products that ultimately will be regulated by the FDA.¹⁶³ Due to significant overlap, the DHHS regulations and the FDA regulations (jointly “federal regulations”) will be summarized together.

Under the federal regulations, scientists using human subjects in research must obtain informed consent. Informed consent requires scientists to fully disclose all relevant benefits, risks, and potential adverse effects when performing experiments on human subjects.¹⁶⁴ Subjects must be allowed to withdraw at any point with no penalty or loss of benefits to which the subject is otherwise entitled.¹⁶⁵ Scientists must be able to produce written documentation of such informed consent before the experiment may proceed.¹⁶⁶ If a proposed subject is incompetent to make an informed choice, a scientist may seek consent from a third party

¹⁶⁰ International Covenant of Civil and Political Rights, 1966.

¹⁶¹ DENNIS M. MALONEY, PROTECTION OF HUMAN RESEARCH SUBJECTS 11 (1984).

¹⁶² 45 C.F.R. § 46.101(a) (1991).

¹⁶³ 45 C.F.R. § 50.1(a) (1991).

¹⁶⁴ 45 CFR § 46.116 (1991); 21 CFR § 50.25 (1991).

¹⁶⁵ *Id.*

¹⁶⁶ 45 CFR § 46.117 (1991); 21 CFR § 50.27 (1996).

who understands the person and will act in his or her best interests. However, if a scientist wants to use members of a vulnerable population as test subjects, he or she must establish the necessity of doing so.

The FDA and DHHS have authorized Institutional Review Boards ("IRBs") to approve or disapprove trials involving human subjects.¹⁶⁷ IRBs generally are comprised of five or more people of diverse backgrounds who review scientific protocols and safeguard the human rights of participants. Their aim is to ensure that risks are minimized and reasonable when compared with anticipated benefits of the proposed experiment. IRBs also ensure that scientists procure informed consent from subjects or their legally-authorized representatives. If the scientist cannot obtain legally effective informed consent from a subject, an IRB must review the experiment to determine whether it can proceed with the subject. An IRB can waive the informed consent requirement only if the experiment involves minimal risk to the subject.

EUROPE

In 1997, the Council of Europe adopted the Convention on Human Rights and Biomedicine ("CHRB").¹⁶⁸ Recognizing "the primacy of the human being" in medical research, the CHRB requires a scientist to obtain informed consent before engaging in human experimentation. Every trial participant must receive information regarding the "purpose and nature of the intervention as well as on its consequences and risks." The CHRB requires heightened standards of informed consent when the trial is non-therapeutic. The CHRB also prohibits non-therapeutic trials involving subjects incapable of giving free consent unless the research aims to benefit the person concerned, or persons in the same age category with the same disease, disorder, or condition. The CHRB includes an exception to the informed consent requirement for research that is therapeutic and informed consent cannot be obtained.¹⁶⁹

¹⁶⁷ 45 CFR § 46.107; 21 C.F.R. §56 .

¹⁶⁸ *Convention on Human Rights and Biomedicine and Explanatory Report*, Council of Europe Doc. DIR/JUR (97) 1, Jan. 1997 reprinted in 36 I.L.M. 817, 821 (1997).

¹⁶⁹ *Id.*, at art. 6(1).

HOW THE DOCTRINE OF INFORMED CONSENT APPLIES TO HIV VACCINE TRIALS

As explained above, the doctrine of informed consent requires scientists conducting HIV vaccine trials to discuss the risks and benefits of participation prior to proceeding with inoculation.¹⁷⁰ An experiment in which scientists fail to discuss all risks and benefits—including access—prior to securing consent is both illegal and unethical. Before any such discussion occurs, the participant must be identified.

This article argues that there are two levels of participation in international HIV trials. One layer of participation is formed by the individuals who must determine whether to allow testing upon their bodies. A second layer of participation is formed by the host country, whose infrastructure, resources, and good will is used in the experiment. Host countries must understand the risks and benefits of participation in order to determine whether to allow pharmaceutical companies to conduct vaccine trials within their boundaries. Under this paradigm, two layers of informed consent are required, and the benefits and risks of the trials must be disclosed to the host country and to the individual participants.

Below is a brief description of some of the risks and benefits that currently may accompany participation in HIV vaccine trials. A review of the risks and benefits of trial participation highlights that while there are real risks inherent in HIV vaccine trial participation, the only real benefit to trial participation at this stage is eventual access to an effective product, assuming one ultimately is developed. For this reason, the issue of access must be included in any discussion of informed consent.

RISKS

Risk denotes the probability that a future harm may occur.¹⁷¹ This harm can be psychological, economic, social, or physical.¹⁷²

¹⁷⁰ See, e.g., The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research*; Grady, *supra* note 26, at 39.

¹⁷¹ Levine, *supra* note 131, at 37.

¹⁷² *Id.* at 49.

This section explores some of the risks individual subjects and host countries face in HIV vaccine inoculation.

RISKS TO SUBJECTS

Thus far, HIV vaccine candidates have been, for the most part, recombinant vaccines genetically engineered from protein particles found on the envelop of the HIV antigen. Accordingly, this discussion will be confined to discussion of genetically-engineered vaccines. As opposed to whole killed or live attenuated vaccines, there is little chance of becoming infected from inoculation with a genetically-engineered vaccine.

Other health risks remain. For example, due to physiological reactions known as immuno-suppression or immune tolerance, individuals who are inoculated with a genetically-engineered vaccine may not be able to mount a sufficient response against other HIV strains. For this reason, inoculated individuals may experience a more rapid progression of the disease should he or she later become infected with the virus.¹⁷³

Individuals risk antibody-enhanced infectivity, which means they are more easily infected and more likely to experience a shorter incubation period and suffer a more virulent form of the disease upon infection.¹⁷⁴ Participants also risk a systemic reaction to the inoculation itself, which could result in anything from mild flu-like symptoms to guillain-barre syndrome, a neurological reaction that could result in paralysis.¹⁷⁵ Of course, unknown unexpected risks may later present problems.¹⁷⁶

Another risk is the vaccine will effectively stimulate HIV antibody production. As most readily-available and inexpensive HIV tests detect the presence of antibodies rather than the virus itself, recipients of antibody stimulating vaccines will test HIV-positive. They will not know whether the presence of antibodies is due to the inoculation or the virus. As a result, it will be difficult for participants to determine their HIV status. Moreover,

¹⁷³ THOMAS A. KERNS, *ETHICAL ISSUES IN HIV VACCINE TRIALS* 123 (1997).

¹⁷⁴ *Id.* at 125.

¹⁷⁵ *Id.*

¹⁷⁶ Karen Auge, *Denver Public Health Tests Early AIDS Vaccine*, DENVER POST, Feb. 12, 2003, available at 2003 WL 5506538.

the presence of antibodies could leave participants vulnerable to discrimination.¹⁷⁷

Participants face other, non-physical, risks. For example, many scientists fear that inoculation with an experimental HIV vaccine could encourage a false sense of security. Those who participate in HIV vaccine studies could mistakenly believe themselves to be protected against AIDS and consequently increase high-risk behavior.¹⁷⁸ Ironically, vaccination could indirectly increase their risk of being infected. Although in theory this side-effect could be mitigated, education has proven ineffective in reducing high-risk behavior among certain populations.¹⁷⁹

Participants also will be inconvenienced by the rigors of trial compliance. Volunteers may be required to endure numerous shots over a several-year period. They will be obligated to return on numerous occasions for testing and monitoring. During these visits, they will be expected to answer detailed questions about their sex-lives, which no doubt may cause some embarrassment.¹⁸⁰ In addition, participants may be unable to bear children for a certain period.¹⁸¹

Finally, individuals who participate in a vaccine trial will likely be unable to participate in later trials involving experimental treatment should they later contract HIV. Early participation likewise may preclude participation in a later trial with a more effective vaccine.¹⁸²

¹⁷⁷ *Perspectives*, *supra* note 41; see also Remarks by Miriam Maluwa, *AIDS in National and International Law*, 96 AM. SOC'Y INT'L. PROC. 320, 322 (2002). This risk could be countered by providing participants with official documentation stating that they are HIV-positive due to participation in the vaccine trial, rather than due to presence of the virus. *Id.*

¹⁷⁸ *The WHO and Why of HIV Vaccine Trials*, *supra* note 46, at 313; *Perspectives*, *supra* note 41.

¹⁷⁹ Raja Mishra, *Results Coming Soon on Human Trial of Anti-AIDS Vaccine*, DESERT NEWS, Dec. 25, 2002, available at 2002 WL 104068062.

¹⁸⁰ *Id.*

¹⁸¹ Mayrav Saar, *A Worthwhile Test of Hope*, ORANGE COUNTY REG., March 2, 2003, available at 2003 WL 6988121.

¹⁸² Jesse Green, *Who Put The Lid On GP 120*, N. Y. Times, Mar. 26, 1995.

RISKS TO HOST COUNTRIES

Host countries also face specific risks by allowing pharmaceutical companies to conduct trials within their borders. As explained above, trial participation could augment the AIDS crisis by inadvertently encouraging high-risk behavior. This could lead to an even more serious health crisis that further undermines the local economies. In addition, vaccine trials would require participants to miss work, thereby detracting from economic growth. Also, host governments could squander the good-will of their populations if the trials are unsuccessful, or if participants are precluded from hosting later trials due to their participation in early trials for ineffective products. But perhaps most importantly, host countries risk severe political fall-out if they agree to participate in trials for a product that their citizens cannot afford when it becomes available to the North.

BENEFITS

Informed, autonomous individuals presumably would not agree to participate in vaccine trials unless they in-turn receive sufficient benefits.¹⁸³ In therapeutic trials, participants often benefit directly through participation. Because participation results in medical treatment, subjects receive a health benefit directly from the product being tested. In fact, because there is no cure for AIDS, and because treatments are often unaffordable to individuals in developing countries, the best hope of treatment for someone who contracts HIV in the South may be participation in an experimental drug trial.

When a vaccine being tested does not provide treatment and is not likely to provide immunity, inoculation provides no direct benefit to the participant. Although the efficacy of some vaccines proceeding to Phase III trials may be unknown, it is not

¹⁸³ It is worth noting that bioethical norms prohibit pharmaceutical companies from paying participants anything other than a modest stipend. *See, e.g.*, CIOMS Guideline 4. It is widely believed that to pay individuals to participate in drug trials would be unduly coercive. Generally, bioethical codes dictate that subjects can be compensated for their inconvenience, time spent, and expenses, but not so much to induce subjects to participate in research against their better judgment. *See, e.g.*, CIOMS Guideline 7; Kerns, *supra* note 173, at 74. Whether or not this is an appropriate prohibition is outside the scope of this paper. It is an assumption of this article that pharmaceutical companies may not pay anything other than a modest stipend to participants.

anticipated at this stage that vaccines currently in trial will prevent infection. Because trial participants are high-risk, and an effective vaccine is likely at least five years away, it is statistically likely that any participant from a high-risk population will contract the virus before an effective vaccine is developed. For these reasons, participants are unlikely to benefit directly from the vaccine themselves.

There is one significant indirect benefit to trial participation. Assisting in the development of a vaccine may help others. Some individuals may be willing to accept risks in order to help develop a vaccine that benefits their families and communities.¹⁸⁴ In so doing, they could psychologically benefit from voluntarily assisting in the advancement of important humanitarian goals.¹⁸⁵ Under a less individualistic, more communitarian analysis, participation becomes an opportunity to benefit others rather than a burden.¹⁸⁶ This communitarian approach to interpreting benefits may be more appropriate in vaccine studies than in other medical studies, as epidemics affect communities *as communities*, not just individuals.¹⁸⁷ This analysis also could be more appropriate in certain societies where trials are occurring, such as Thailand, where a more communitarian view of an individual's relationship to society may be held.

Many subjects have indicated that they benefit from the psychological lift they get from helping someone else, even if they do not directly benefit from the trials.¹⁸⁸ There is little reason to believe that individuals in the South would benefit psychologically from serving as a human laboratory for the North, to assist in the development of a product that will not save the lives of their friends and families because they cannot afford it. Any psychological benefit from participation would be eviscerated if their communities do not gain access to the vaccine because the

¹⁸⁴ See Grady, *supra* note 26, at 65; see also Evelyn Kiapi Matsamura, *Health-Uganda: Second HIV/AIDS Vaccine Trials Under Way*, INTER PRESS SERVICE, Feb. 12, 2003, available at 2003 WL 6914128 (noting that Ugandan trial participant is willing to "risk his life" in vaccine trials in the hope that he can benefit his community.)

¹⁸⁵ See Grady, *supra* note 26, at 67.

¹⁸⁶ *Id.* at 71.

¹⁸⁷ *Id.* at 72–73.

¹⁸⁸ *Id.* at 20, 56; see also Auge, *supra* note 176.

pharmaceutical companies that seek their participation later deny their communities access to the vaccine by pricing them out of the market.¹⁸⁹

Further, any false beliefs held by the participants that their communities will gain access to the vaccine could result in psychological harm if the vaccine is prohibitively expensive and thus inaccessible. This harm undermines the principles of psychological integrity and self-determination that the doctrine of informed consent aims to promote.¹⁹⁰ Thus, even if participants are not physically harmed by the experiments, they could still experience psychological or emotional harm from any deception, manipulation, or false expectations that induce them to participate.¹⁹¹

Countries may benefit similarly from hosting trials in various ways,¹⁹² but the main benefit for the nation would be access to a vaccine that could help to end a devastating public health crisis within their borders. An inability to gain access to the vaccine they helped to develop would eviscerate this benefit.

HOW ACCESS CAN BE ENHANCED FOR TRIAL PARTICIPANTS THROUGH THE DOCTRINE OF INFORMED CONSENT

Many governments in the South believe themselves to have an affirmative obligation to safeguard the health of their citizens. For example, the International Covenant on Economic, Social, and Cultural Rights provides that each citizen has the “right to the highest attainable standard of physical and mental health.” Some have interpreted this right to require states to take steps necessary for the prevention and treatment of disease.¹⁹³ Although human rights instruments provide aspirational goals that

¹⁸⁹ Although some may suggest that researchers simply should pay volunteers for their participation, this is considered unduly coercive and unethical.

¹⁹⁰ Katz, *supra* note 138, at 323–24.

¹⁹¹ *Id.*

¹⁹² For example, host countries may gain prestige and political good-will for their administrations. Their medical communities may receive valuable training and mentoring and may enjoy enhanced prestige due to participation in an international trial. The community may also enjoy enhanced foreign investment.

¹⁹³ J.M. Spectar, *The Hydra Hath But One Head: The Socio-Cultural Dimensions of the AIDS Epidemic & Women's Right to Health*, 21 B.C. THIRD WORLD L. J. 1, 14–15 (2001).

impose no affirmative obligations, many states take seriously the obligations created by such documents and believe that states have a duty to take whatever steps they can to prevent or reduce serious health threats.¹⁹⁴

Certainly, one could argue that the “right to health” embodied in human rights instruments requires states to use whatever resources and leverage they have to ensure that their citizens gain access to vaccines that could save their lives. One way governments could help fulfill these goals is by refusing to host international vaccine trials unless the pharmaceutical companies involved take certain steps to ensure that the host countries will receive access to any vaccine the pharmaceutical company develops, either directly or indirectly, through their participation.

Because individual participants, as well as the host countries, often view access to the vaccine as a key benefit of trial participation, the doctrine of informed consent requires scientists to clearly disclose in advance the steps planned to provide access. Requiring pharmaceutical companies to articulate a plan when they still need to encourage participation will increase the likelihood of ethical behavior and enhance the autonomy that informed consent was designed to protect. Delineating any proposed measures to achieve access before trials begin will help ensure and fulfill the expectations of all parties. It will also make sure that steps are taken when there is still time to implement whatever plans are agreed upon to ensure access – such as the construction of additional factories, the building of roads, or the earmarking of funds by the pharmaceutical company. Additionally, because no one gains from deterring drug trials from occurring, steps to achieve access should be negotiated on a case by case basis, rather than legislated, thus maximizing choice and autonomy for all involved, and allowing market principles to ensure that the most efficient agreements are reached. If the pharmaceutical company does not agree to take sufficient measures in the eyes of the host country, it can refuse to participate, and the host population will remain free to test other vaccines produced by other pharmaceutical companies.

But, in keeping with the goal of autonomy and allowing for the fulfillment of market principles, this article does not suggest

¹⁹⁴ *Id.* at 15–16.

legislative dictates regarding what steps the parties should agree upon before trials should proceed.¹⁹⁵ Rather, the host countries and the pharmaceutical companies should together determine what steps are desirable and feasible. In this way, market principles will provide efficient results. No country will participate without achieving a base level of benefits, and pharmaceutical companies will not pursue trials in a particular country if doing so would be prohibitively expensive.

The benefits of this approach are threefold. First, it reduces the chance of exploitation. Because pharmaceutical companies need to test their vaccines on high-risk, HIV negative volunteers, they require the participation of the developing world, which encompasses many such populations. There is a tendency on part of many pharmaceutical companies to view developing countries as partners when they want to run drug trials within their borders, but to treat them as beggars when later discussing access to the drugs developed. By discussing access in advance, host countries can approach negotiations as equal parties with something to offer as well as something to gain.¹⁹⁶ And, by discussing access before host countries or subjects agree to participate, scientists can fulfill the principles of informed consent and insure that no deception or false expectations regarding eventual access improperly induces participation. By including access as part of the informed consent process, scientists will ensure that every participant is able to make a decision regarding participation that is in line with his or her own preferences, thereby enhancing self-determination in a way that complies with the underlying principles of informed consent. They further will prevent any psychological

¹⁹⁵ An outline of possible approaches is presented in the appendix of this paper.

¹⁹⁶ Some have suggested that developing countries may lack the bargaining power necessary to ensure vaccine access through trial participation. This view may underestimate the sophistication of developing countries, which have faced this epidemic for over twenty years and have exacting significant concessions from the pharmaceutical industry. For example, they were able to exact concessions in TRIPS allowing exportation of generics produced pursuant to compulsory licenses. Moreover, any negotiating process that occurs as part of the informed consent process would be monitored by international funding organizations and non-governmental organizations that lobby in favor of drug access in the developing world. In this era of transparency and accountability, developing countries will not face pharmaceutical companies alone. Instead, they will be buttressed by sophisticated international organizations who have lobbied tirelessly in favor of access ever since TRIPS came into effect.

or emotional harm that would result if the participants' expectations regarding access are not fulfilled when the experiments are concluded.¹⁹⁷

Second, this approach will force parties to think about the issue of access in advance. In the rush to move forward with vaccine trials, details of access plans often are not worked out. Given the history of pharmaceutical testing in the developing world, this may be exactly the wrong approach. Because of the time lag between when promises are made, when participation occurs, and when a vaccine could be available, pharmaceuticals could make vague and unenforceable promises to induce participation, without any intention of or means by which to enforce such promises.

Even pharmaceutical companies with the best intentions may run into difficulties when attempting to negotiate access after a drug is developed. For example, a company may intend to provide free or subsidized vaccine, but may find itself with insufficient funds to do so unless adequate steps are taken in advance. Alternatively, a company may find that in order to recoup its costs, its factories must produce only vaccine that can be sold at market rate.

Arguing after-the-fact about who can gain access to the vaccine and at what cost wastes time, money, and resources that could be better spent elsewhere. By negotiating access as part of the informed consent process, host countries will hold an enforceable, written contract under which they can hold pharmaceutical companies to their promises.¹⁹⁸ Further, by negotiating in advance, both parties can plan ahead and take whatever steps are necessary to fulfill their commitments. Pharmaceutical companies will not be faced with demands that they cannot reasonably meet, and host countries will not be denied what they feel they are due. Pharmaceutical companies will avoid creating the

¹⁹⁷ See, e.g., Katz, *supra* note 138, at 323–24.

¹⁹⁸ The contract would be secured in writing because informed consent generally requires written documentation. The parties may wish to include a choice of forum clause should a dispute arise.

ill-will that has haunted them in the past and that has undermined their subsequent ability to recruit trial participants in certain communities.¹⁹⁹

Finally, this approach is beneficial in that it does not require the passage of any new law. Rather, it simply recognizes that access is one of the benefits that must be discussed under the doctrine of informed consent.

Funding agencies, nongovernmental organizations, and host countries are in a position to apply an expansive interpretation of the doctrine and demand a discussion of access prior to commencement of trials. Funding agencies could refuse to fund pharmaceuticals that do not negotiate access prior to commencing trials. Host countries can use their power by refusing to allow trials unless the issue of access is negotiated in advance. Governments can amend their protocol requirements, so that each pharmaceutical must include an initial discussion of access as part of the process. As more countries and funding institutions adopt and enforce this expansive view of informed consent, a discussion of access will begin to occur as a matter of course. If the doctrine of informed consent is to have any meaning in the context of international HIV trials, no less can be demanded.

CONCLUSION

As more vaccine candidates enter Phase III trials, pharmaceuticals companies will be forced to compete for the high-risk

¹⁹⁹ An example of such ill-will is found among certain African-Americans in the United States. From 1932 to 1972, scientists in the Tuskegee syphilis study, conducted under the auspices of the federal government, withheld medical treatment from poor, African American men who had syphilis, in order to study the course of the disease. The men were not treated with penicillin after it became available. Ultimately, 128 died from syphilis or related complications during the course of the experiments. Some African-American activists posit that as a result of this abuse, it is difficult to recruit African-Americans to participate in drug trials. Deborah Kong, *Blacks' mistrust stymies AIDS study*, MIL. J. SENT., Mar. 3, 2003, available at 2003 WL 3307415. This difficulty creates problems for scientists who need to test drugs among the African-American community. For example, when VaxGen tested its HIV vaccine, it found that the vaccine, which was generally ineffective, showed some signs of effectiveness among African-Americans. The African-American trial population, however, was so small that it was difficult to determine the statistical significance of the result. Sabin Russell & Tom Abate, *Scientists Split Over Role of Race in AIDS Vaccine*, S. F. CHRON., Feb. 25, 2003, available at 2003 WL 3748557.

volunteers. These volunteers often have only one shot to participate in trials. Pharmaceutical companies can compete with each other by offering better terms regarding access. Participants will not be in the position of receiving charity after a vaccine is developed. Rather, in exchange for their services and participation, they will be entitled to the benefit of access.

By suggesting a procedure, rather than the substance of an agreement, this proposal supports the principle of autonomy and avoids paternalism by allowing participants with relatively equal bargaining power to design the substance of the exchange themselves. It will also help avoid the stain of exploitation that has plagued international trials in the past.

This approach maximizes individual autonomy, deters fraud, encourages rational decision making, and promotes equity and fairness. Furthermore, such an approach will help to cultivate an atmosphere of trust between the North and the South and enable a strengthened partnership on the path to finding an effective HIV vaccine.

APPENDIX

This paper has suggested that the doctrine of informed consent can be interpreted expansively to help ensure HIV vaccine access to trial participants. It has advocated an approach and a process rather than a particular benefit that must be supplied to participants. Nonetheless, it does raise certain questions about what some of the possible approaches to access could be. This appendix will briefly discuss some of the many options upon which the parties agree to better ensure access.

Companies could agree to provide vaccine dosages to the host country for a certain period. They could voluntarily grant a license to allow generic production within the host country. They could also engage in technology transfer and infrastructure building so that generic production is possible.²⁰⁰ Alternatively, they

²⁰⁰ Technology sharing, combined with a license to manufacture the vaccine locally, could better enable long-term access. It also promotes a local competitive generic drug industry and could result in technology transfer, generating additional jobs and development.

could allow third party contractors to bid on AIDS vaccine production if the country lacks the infrastructure to produce the vaccine itself.

Pharmaceutical companies could also contribute to an international trust fund to be activated when an effective vaccine is developed. For example, they could contribute to a purchase fund, such as the one sponsored by the International AIDS Vaccine Initiative (“IAVI”).²⁰¹

A pharmaceutical company could grant a percentage of net royalties to the host country. For example, the IAVI subsidizes firms engaged in vaccine trials and has invested approximately \$15 million to create vaccine development partnerships. Through these partnerships, IAVI secures distribution rights should the company decline to produce the vaccine for developing countries in reasonable quantity at a reasonable price. IAVI retains the rights to contract with other manufacturers to make the vaccine available. In exchange, the firms agree that they will supply any product developed at a reduced profit margin. IAVI is currently sponsoring vaccine trials in Kenya. Another example is provided by the Samoan government. Scientists utilized bark found in Samoa to develop the anti-HIV drug prostratin with cooperation of village chiefs in exchange for 20 percent of the profits.

The breadth of these approaches further supports the argument that the parties should decide for themselves on a case-by-case basis how – and to what extent—they will ensure access to vaccine trial participants. Parties that adopt creative approaches will provide examples to other countries and companies engaged in the informed consent, negotiating process.

²⁰¹ Some countries may not agree to this approach without concomitant price controls, because creating a fund simply puts money back in pockets of drug companies. Moreover, a purchase fund would tie up capital for an undetermined amount of time – but likely to be at least ten years – until an effective candidate can be mass-produced. This capital could be better used to advance public health objectives in the short-term.

