

# CHALLENGES FOR INTELLECTUAL PROPERTY MANAGEMENT OF HIV VACCINE-RELATED RESEARCH AND DEVELOPMENT\*: PART 1, THE GLOBAL CONTEXT

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The HIV/AIDS<sup>1</sup> pandemic is one of the defining issues of the 21<sup>st</sup> century.<sup>2</sup> AIDS is the leading cause of death in Africa and the fourth-leading cause of death globally.<sup>3</sup> UNAIDS estimated that 33.2 million people were living with HIV in 2007.<sup>4</sup> More than twenty million people have already died from AIDS and sixty-five million will face death over the next twenty years.<sup>5</sup> The majority of these live in the developing world among the world's poor, powerless and marginalized.

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1 HIV stands for human immunodeficiency virus and AIDS stands for acute immunodeficiency syndrome.

2 Justice Edwin Cameron, "Opening Commentary" (Remarks presented to the XIV International AIDS Conference, Barcelona, Spain, July 2002) [unpublished]. The human immunodeficiency virus (HIV) is made up of genetic material called RNA - hence it is a retro-virus. Many people with HIV may have few or no signs or symptoms of the disease for up to 10 years. As time passes, the HIV infection damages the person's immune system. At this point, a person may develop AIDS or acquired immune deficiency syndrome. An official diagnosis of AIDS in Canada is given when a person with HIV develops one or more opportunistic infections or certain cancers that are rare in the general population and characteristic of people infected with HIV. Lark Lands & Deirdre Maclean, *A Practical Guide to HAART (Highly Active Anti-Retroviral Therapy)* (Toronto: CATIE, 2002), online: CATIE <[http://www.catie.ca/PG\\_HAART\\_e.nsf/toc/7BDD5BFABD5396C085256B8B005A119B?OpenDocument](http://www.catie.ca/PG_HAART_e.nsf/toc/7BDD5BFABD5396C085256B8B005A119B?OpenDocument)>..

3 The Global Fund, *HIV/AIDS Background*, online: The Global Fund <<http://www.theglobalfund.org/en/hivaids/background/?lang=en>>.

4 UNAIDS, *07 AIDS epidemic update* (Geneva: WHO, 2007) online: UNAIDS <[http://data.unaids.org/pub/EPISlides/2007/2007\\_epiupdate\\_en.pdf](http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf)>.

5 The Global Fund, *supra* note 3.

Despite the increased focus on the global AIDS pandemic since the XIII International AIDS Conference in Durban, South Africa in July 2000, and despite some very significant developments since that time, the vast majority of people living with HIV/AIDS still lack access to affordable and effective treatment programs and medications.<sup>6</sup> The best long-term hope for controlling HIV/AIDS, therefore, is the development and widespread distribution of a safe, effective and affordable vaccine.

Research into vaccines is in accord with the *Declaration of Commitment on HIV/AIDS*, signed in June 2001 by 189 member states of the United Nations. The declaration recognized the need for a strong global response to the AIDS epidemic and, as part of that response, the need for HIV vaccine research, development and access. The Declaration committed member states to:

[e]ncourage increased investment in HIV/AIDS-related research, nationally, regionally and internationally, in particular for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides, and encourage the proactive preparation of financial and logistic plans to facilitate rapid access to vaccines when they become available.<sup>7</sup>

Unfortunately, despite more than twenty years of research, no effective HIV vaccine aimed at either prevention or treatment of infected individuals has been forthcoming for either the developed or developing world. On the promising front, in the last ten years, three developments have helped accelerate HIV vaccine Research and Development (R&D). The first is the creation of public-private partnerships (PPPs) that capitalize on the strengths of the public and private sectors such as the International AIDS Vaccine Initiative (IAVI) and the Global Aids Vaccine Alliance launched in 2000 (GAVI); the second is the global connection of researchers, government agencies and international organizations under the Global HIV/AIDS Vaccine Enterprise (GHAVE) with an aim to coordinating research, knowledge sharing and capacity building; and the third is the infusion of funding spearheaded by philanthropic partners including the Bill & Melinda Gates Foundation (the

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6 Richard Elliott *et al.* "Global Treatment Access: Legal Developments and Challenges" (Paper presented to the XIV International AIDS Conference, Barcelona, Spain, July 2002) [unpublished]; Richard Elliott *et al.*, *Putting Third First: Vaccines, Access to Treatment & the Law* (Montreal: Canadian HIV/AIDS Legal Network, 2002).

7 *Declaration of Commitment on HIV/AIDS*, 26th Spec. Sess., Annex, Agenda Item 8, UN Doc. A/RES/S-26/2 (2001) at para. 89.

Gates Foundation) and the creation of PPPs such as the United States' Collaboration for AIDS Vaccine Discovery (CAVD).

Considerable research is being conducted and better coordinated at the global level now, with the hope that one or more vaccine candidates will emerge in the next decade. Of great concern to those in the research and funding enterprise is ensuring global access to vaccines and related products once they are developed. That access is particularly important in the developing world where AIDS continues to kill and infect millions of men, women and children. Balancing the need to provide incentives for R&D of HIV vaccines with the need for affordable global access to those vaccines is one of the most pressing challenges in international public health. A critical factor in this balancing act is the management of intellectual property rights (IPRs).

Here we discuss potential roadblocks to the coordinated international efforts for HIV vaccine development and, in particular, potential roadblocks caused by IPRs in the process of vaccine development and potential roadblocks caused by IPRs to global access to vaccines, once developed. In our second, companion paper, we discuss the same issues from a Canadian perspective.<sup>8</sup> This paper is divided into four sections. Part one lays out the background issues for managing and coordinating international vaccine research. It covers some differences between vaccine and pharmaceutical R&D, outlines HIV vaccine R&D to date and lays out the intellectual property (IP) issues most relevant to HIV vaccine R&D. Part two outlines IP management techniques that can be used to avoid blockage to research tools or IP blocks to on-going research projects. Part three outlines IP management strategies that can be used to ensure global access to the outcomes of funded research projects. We conclude with a summary of strategies available to governments (through funding agencies or otherwise) to encourage HIV vaccine research and to ensure global access to the products and processes produced by that research.

The issues raised through our research were discussed with twelve international experts and their contributions are acknowledged throughout the paper.<sup>9</sup>

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8 San Patten, Tania Bubela, & Lori Knowles, "Challenges for Intellectual Property Management of HIV Vaccine-Related Research and Development: Part 2, the Canadian Context" (2008) 16 Health L.J. (in press).

9 Key informants were: Erik Iverson, Associate General Council, Bill & Melinda

## Part 1: Background Issues for Managing and Coordinating International Vaccine Research

### Vaccine versus Pharmaceutical Research and Development

There are significant differences between vaccine and pharmaceutical R&D. Vaccine R&D, especially recombinant vaccine R&D in the case of HIV<sup>10</sup>, can be considerably more complicated than pharmaceutical R&D. The latter involves screening a library of chemical compounds, generally small molecules, in a variety of biochemical and cellular assays to test for the function of interest.<sup>11</sup> Once an active molecule of interest has been identified, studies move into laboratory animals to test for efficacy, toxicity and pharmacokinetics.<sup>12</sup> This allows a pharmaceutical company to decide whether

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Gates Foundation; Steven Ferguson, Office of Technology Transfer, Nation Institutes of Health; Labeeb M. Abboud, General Counsel International AIDS Vaccine Initiative; Jackie Quay, CHAVI Director of Intellectual Property, Duke Human Vaccine Institute, Durham NC; Robert Hecht, Senior VP, Policy Dept, IAVI; Lidwien van der Valk, Legal Advisor, European and Developing Country Clinical Trials Partnership; Richard Wilder, Sidley Austin, Washington DC; Louis C. Cullman, Louis C. Cullman, Esq., Partner, Intellectual Property, K&L Gates; Steven Wakefield, Associate Director for Community Relations and Education, HVTN (HIV Vaccine Trials Network); Arti Rai, Elvin R. Lattey Professor of Law, Duke University; Robert Cook-Deegan, MD, Director, Center for Genome Ethics, Law, and Policy, Institute for Genome Sciences and Policy, Duke University; John H. Barton, George E. Osborne Professor of Law, Emeritus, Stanford Law School.

10 Recombinant vaccines are made by inserting a gene for a desired antigen (a foreign substance capable of triggering an immune response in an organism) into a vector, usually a virus that has low virulence meaning that it has little ability to cause disease. The vector expressing the desired antigen may be used as the vaccine or the antigen may be purified and injected as a subunit vaccine. Recombinant viruses are generally safe, have few impurities and have low production costs, but are costly to develop because of the complexity of the research involved. The only recombinant vaccines currently in use in humans are the Hepatitis B Virus (HBV) vaccine and the Human Papillomavirus (HPV) vaccine.

11 Anthony Li, "NIH chemical genomics network takes off" (2004) 9 Drug Discovery Today 685.

12 How the substance is absorbed and metabolized by and excreted from the body.

the molecule is worth testing in human subjects from preliminary trials in a small number of individuals to large-scale clinical trials.<sup>13</sup> Recombinant vaccine development, on the other hand, is much more complex; it requires antigen and vector platforms and a host of other technologies including purification, expression, stability and delivery technologies.

Depending on the stage of research and on the vaccine in question, it may be necessary to have access to cross-cutting technologies such as expression systems, fusion partners, adjuvant systems, excipients and delivery systems or devices.<sup>14</sup> With regard to delivery systems, the biological nature of vaccines requires production processes to ensure quality and potency that are often more complex and costly than those used in pharmaceutical production. For many vaccines, delivery systems, especially those requiring cold storage, are more complicated than those required for chemical medicines. Similarly, conducting clinical trials and obtaining regulatory approval particularly for new classes of vaccines may be more costly and time consuming.

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13 For an interactive chart of the new drug development process, steps from test tube to new drug application review see U.S. Food and Drug Administration, *The New Drug Development Process: Steps from Test Tube to New Drug Application Review*, online: FDA <<http://www.fda.gov/cder/handbook/develop.htm>>. For problems with the current drug development process see: U.S. Department of Health and Human Services, Food and Drug Administration, *Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004) online: FDA <<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>>.

14 Access to Technologies Team of the Department of Immunization, Vaccines and Biologicals, *Intellectual Property Rights and Immunization: Meeting Report 19-20 April 2004* (Geneva: WHO, 2004) online: WHO <[http://whqlibdoc.who.int/hq/2004/WHO\\_IVB\\_04.21\\_\(302KB\).pdf](http://whqlibdoc.who.int/hq/2004/WHO_IVB_04.21_(302KB).pdf)> at 12 [IVB]. In the IAVI glossary of terms for HIV Vaccine Development, an expression system is defined as follows: "In genetic engineering, the cells into which a gene has been inserted, with the aim of producing its encoded protein. Chinese hamster ovary (CHO) cells and baculovirus/insect cells are two expression systems often used to make recombinant HIV vaccines" (International AIDS Vaccine Initiative, *AIDS Vaccine Glossary*, online: IAVI <<http://www.iavi.org/viewpage.cfm?aid=34>>). An adjuvant is defined as "[a] substance sometimes included in a vaccine formulation to enhance or modify its immune-stimulating properties." Die.net online dictionary defines "excipient" as "an inert or slightly active substance used in preparing remedies as a vehicle or medium of administration for the medicinal agents" (Die.net, "Definition: excipient," online: Die.net <<http://dictionary.die.net/excipient>>).

Another salient difference, particularly in the United States, is that vaccines are not subject to bioequivalence standards, and therefore successful vaccine development is dependent on having the capacity required to demonstrate equivalence. Bioequivalence standards streamline the entry of generic pharmaceuticals into the marketplace.<sup>15</sup> Such regulations exist in most jurisdictions and provide a simplified approval process based on the proof of “essential similarity” or product equivalence of a generic pharmaceutical compared to the patented pharmaceutical already available in the market place. Equivalency may be in terms of chemical composition, pharmaceutical equivalence or dosage forms, and therapeutic equivalence. Generic pharmaceuticals are almost identical to the original product or contain an active ingredient for which the patent has expired.<sup>16</sup> In the case of vaccines, however, to obtain regulatory approval each manufacturer must provide their own clinical trial data which is both time consuming and costly.

Finally, a much smaller market exists for vaccines than for pharmaceuticals, and, if a vaccine is successful, there may be no return market. Unlike pharmaceutical manufacturing, the public sector has historically been a key partner in vaccine production, pricing and marketing. The goal of the public sector is to ensure increased public health. This public welfare goal is fulfilled by maximizing access to essential medicines and vaccines. The public sector is therefore, committed to keeping prices of vaccines as low as possible to ensure broad access and proper use of public funds. In contrast, private sector development of pharmaceuticals and vaccines has, as its ultimate goal, to ensure a return on investment.

While these goals are in conflict, it is possible with clearly articulated partnership terms and project goals, to leverage the relative strengths of both sectors in vaccine development. In fact, the involvement of both sectors in the development of many vaccines is crucial if vaccine candidates are to move swiftly from research to development to market. Given the complex-

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15 David Dudzinski, “Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies” (2005) 60 Food & Drug L.J. 143; Enrico Polastro & Arthur D. Little International Inc., *Biogenerics: myth or reality?*, online: IPT online <<http://www.iptonline.com/articles/public/IPTNINE63NoPrint.pdf>>; Selena Class, *Biogenerics: Waiting for the Green Light*, online: IMS Company Profiles <[http://www.imshealth.com/web/content/0,3148,64576068\\_63872702\\_70261006\\_71226827,00.html](http://www.imshealth.com/web/content/0,3148,64576068_63872702_70261006_71226827,00.html)>.

16 Dudzinski, *supra* note 15.

ity of many viruses and vaccines and the lack of strong market incentives where there are large developing country markets, other incentives are needed to induce private sector partners into these very long-term vaccine R&D ventures. One incentive is the ability to patent research products. This is a greater incentive where the vaccine will also have a developed country market, such as HIV/AIDS vaccines. There are other strategies that can be employed to bring private sector partners into vaccine development and still ensure vaccines make it to the less lucrative developing country markets. These strategies are discussed *infra* in parts 2 and 3.

### The global landscape of HIV vaccine research and clinical trials

Complicating the IPR issues in HIV vaccine research is the global scale of the research collaborations which often involve parties from both the private and public sector. The involvement of public private partnerships (PPPs), to function as product development partnerships (PDPs), leverages the expertise of both sectors. PPPs enjoy certain advantages that academic technology managers and other traditional partners might not have. PPPs are flexible and have broad capacity to identify and work with partners in both public and private sectors. Added to this is a strong focus on rapid product development that is not hindered by a need to secure the maximum return on investment because of public or philanthropic funding.

In the world of HIV vaccine development, PPPs such as IAVI have become extremely influential. Although most vaccine-related PPPs share similar goals, their size, complexity and business models vary. One of the largest PPPs is the CAVD funded by sixteen separate grants from the Gates Foundation. In the CAVD there are eleven candidate vaccine projects. Collaboration has been built into the very fabric of the PPP. There is a high expectation for the sharing of data and collaboration between what ultimately will be competing projects. Some PPPs are geared only to conducting clinical trials, others conduct in-house product development, while others manage collaborative development by public and private laboratories.<sup>17</sup>

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17 Major PPPs in this field include: IAVI, the AIDS Vaccine Advocacy Coalition (AVAC), CAVD, the Center for AIDS/HIV Vaccine Immunology (CHAVI), GAVI, the African AIDS Vaccine Programme (AAVP), the South African AIDS Vaccine Initiative (SAAVI), and the European and Developing Countries Clinical Trials Partnership (EDCTP).

Some companies, academic institutions and public foundations are farther down the vaccine development pipeline as evidenced by existing clinical trials.<sup>18</sup> Unfortunately, two highly publicized vaccine trials, the Step Study, were prematurely terminated in September 2007. The vaccine made by Merck and Co. actually increased the risk of HIV infection in some study participants (those with high levels of antibodies to the virus which causes the common cold, adenovirus 5 (Ad5) and a component of the vaccine) and was ineffective in the rest of study participants.<sup>19</sup> Indeed, on October 23, 2007, the South African AIDS Vaccine Initiative (SAAVI) announced that, based on recommendations made by an independent Data and Safety Monitoring Board, it was permanently suspending immunisations and enrolment in a study in South Africa which was evaluating the same Merck HIV vaccine as used in the Step Study.<sup>20</sup> Clinical trials by NIH VRC, NIAID Alpha Vax, PharmaexaEpimmune, and University of Pennsylvania also needed to be re-evaluated in light of the results from the Step Study.<sup>21</sup> As of October

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18 Major vaccine producers include, VaxGen, National Institutes of Health VRC, Sanofi-Pasteur, GlaxoSmithKline, Merck, Chiron, Therion, Wyeth, AlphiVax, ParmexaEpimmune, and Geovax. Clinical trials are ongoing in Australia, Canada, Dominican Republic, United States, China, Rwanda, Thailand, Sweden, Kenya, Brazil, Peru, India, Switzerland, Uganda, South Africa, Jamaica, Zambia, Haiti, Puerto Rico, Tanzania, France, the United Kingdom and the Russian Federation.

19 Jon Cohen, "Did Merck's Failed HIV Vaccine Cause Harm?" (2007) 318 Science 1048. The mechanism for this is not understood but it is speculated that people in the high Ad5 antibody group were more vulnerable to HIV because of "immune activation". Cohen writes the following at 1048: "Specifically, HIV establishes an infection by attaching to T cells that have surface receptors known as CD4 and CCR5. Natural infection with Ad5 creates memory blanks of these very T cells, which expand and direct an attack if Ad5 shows up again. Theoretically, the vaccine vector could have activated these memory cells in the same way, creating more targets for HIV." Not only this however, the multi-country trial was halted prematurely after an interim analysis showed that of 83 HIV infections during the course of the study 49 had been given the vaccine and 33 had been given a placebo, i.e., the vaccine did not work.

20 South African AIDS Vaccine Initiative, News Release, "Update on the STEP and Phambili HIV vaccine trials" (23 October, 2007), online: SAAVI <<http://www.saavi.org.za/7press2007.htm>>.

21 Cohen, *supra* note 19.

2008, the NIH lists four preventative HIV vaccine trials that are recruiting participants and one which is not yet recruiting participants.<sup>22</sup>

The majority of funding for HIV vaccine research comes from the United States; Europeans claim to have developed most of the candidate vaccines and most of the volunteers in later stage clinical trials come from developing countries. This truly illustrates the global nature of HIV vaccine research.<sup>23</sup>

### Intellectual Property Issues in HIV Vaccine R&D

As discussed above, vaccine development involves multiple components and processes, making it a particularly difficult research puzzle. If IP is attached to the majority of research components and methods, the impacts may include, increased transaction costs while licenses are negotiated, delays in research and development, and increased costs of research and resultant vaccines, thereby limiting the feasibility of making a vaccine.<sup>24</sup>

In the world of vaccine R&D, two types of IP are of paramount importance: patents and know-how. Patents give the inventor a monopoly right over use and exploitation of an invention in exchange for public disclosure of the invention. Patents may be granted for research tools, methods, components, delivery methods and end products such as pharmaceuticals or vaccines. But vaccine R&D is also dependent on “know-how.” Some of this knowledge and expertise in vaccine discovery and development is held as proprietary trade-secrets such as methods used in the R&D process. However, much know-how also exists as technical and scientific skills, knowledge and personnel capacity.<sup>25</sup> The ability to reproduce a production process may de-

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22 AIDSInfo, A Service of the U.S. Department of Health and Human Services, “Preventive HIV Vaccine Trials (For HIV-negative individuals)”, online: AIDSInfo <<http://www.aidsinfo.nih.gov/Vaccines/search.aspx?linkID=1&status=open&FrmVal=leftMenu&ordNum=1>>.

23 See also The Pipeline Project, *Table of HVTN Vaccine Trials*, online: Center for HIV information <<http://chi.ucsf.edu/vaccines/vaccines?page=vc-03-00>>.

24 IVB, *supra* note 14 at 13.

25 This is apparently the case with meningococcal conjugate vaccine where the IPRs on the conjugation technology are in the public domain “although the know-how rests in the private sector.” In this example, patents on this platform technology do not pose an IP barrier to commercialization; however, tacit knowledge not disclosed through the patent system does. See PATH, “Why the needed vaccines don’t exist,” online: Meningitis Vaccine Project <<http://www.meningvax.org/needed-vaccines.htm>>.

pend on tacit knowledge that is not revealed in public documentation such as patent applications.<sup>26</sup> Where manufacturing is to take place in developing countries, transferring know-how creates capacity in developing countries so that research tools can be effectively exported to places where vaccines are most needed. Such knowledge transfer can be structured contractually into IP management strategies as will be discussed below in Part 2.

The main problem with the plethora of patents in the vaccine research space indicated through patent mapping is the potential for patent thickets (many overlapping patents or stacking patents in an area of research) that may hinder necessary research.<sup>27</sup> Negotiating a patent thicket is both time and resource consuming. For example, the Malaria Vaccine Initiative (MVI) undertook a mapping project that identified 37 different patents related to one antigen, MSP-1. Researchers would have to negotiate with no fewer than eight entities to access this antigen. Such a complicated licensing structure would take years and be very expensive. Plans have been floated to create a MSP-1 patent pool but appear to have been abandoned.<sup>28</sup> A patent pool is created when a number of patent rights held by different owners are brought together and collectively managed. Patent pools can help reduce uncertainty about proceeding in a particular field and transactional costs by reducing negotiating time from multiple parties to one centralized party and by lowering royalty costs. Pools can function such that all IP holders in a pool provide access to each member's IP in exchange for reciprocal rights (sometimes referred to simply as cross-licensing arrangements), or where third party users pay one fee (rather than stacked royalties) for the bundled IP.<sup>29</sup> Such a pool for essential medicines, including fixed dose combination

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26 IVB, *supra* note 14.

27 Michael Heller & Rebecca Eisenberg, "Can patents deter innovation? The anticommons in biomedical research" (1998) 280 Science 698; but see Timothy Caulfield *et al.*, "Evidence and anecdotes: an analysis of human gene patenting controversies" (2006) 24 Nature Biotechnology 1091 arguing that no good evidence exists for the anticommons effect.

28 Personal Communication with Dr. Donald Kelemen, Senior Commercialization Officer, Malaria Vaccine Initiative.

29 US Department of Justice and the Federal Trade Commission, *Antitrust Guidelines for the Licensing of Intellectual Property*, online: U.S. Department of Justice <<http://www.usdoj.gov/atr/public/guidelines/0558.htm>>; Ted J. Ebersole, Marvin C. Guthrie & George A. Goldstein, "Patent Pools as a Solution to the Licensing Problem of Diagnostic Genetics: United States and European perspectives"

AIDS medicines for the developing world was proposed in 2006 by UNICEF, although it has not yet been created.<sup>30</sup>

In the absence of a patent thicket, patents with exclusive licensing terms may exclude use by third parties including public sector or research uses. In such cases those denied access must either invent work-arounds (finding a method to “work around” the blocking IP) or abandon their research all together. Such a situation arose for the Netherlands Vaccine Institute (NVI) when working on a Hib (*Haemophilus influenzae* type b) conjugate vaccine project beginning in 1999. The project was aimed at developing an up-scalable and patent-free production process for the large-scale production of Hib conjugate vaccine, using technology that could be easily transferred to developing countries. After three years of research, the NVI realized that the preferred purification method by cross-flow filtration was blocked by a patent. A more complicated gel-filtration purification method had to be used which increased the time needed to finish the project. Officials from the NVI describe the situation as such: “Due to [the] patent..., we had to follow a more complex separation method such as gel-filtration. We did not try to negotiate with the patent owner..., because we anticipated that this would have delayed the time to market and we did not have the budget and experience to start a legal dispute.”<sup>31</sup> Despite this roadblock, the Hib vaccine production project has been a success story in technology transfer for NVI. The cost of work-arounds may not be high in comparison with overall vaccine development expenses, but it has a negative impact on the development timeframe, adds uncertainty to a project and therefore has a negative impact on costs.<sup>32</sup>

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(2005) Drug Discovery World Spring 86; Jeanne Clarke *et al.*, *Patent Pools: A Solution to the Problem of Access in Biotechnology Patents?*, online: United States Patent and Trademark Office

<<http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>>.

30 International HIV/AIDS Alliance, “‘Patent pools’ will increase access to essential medicines, says Stop AIDS campaign” (2 May 2007), online: AIDS Alliance <<http://www.aidsalliance.org/sw47365.asp>>; see also E. Richard Gold *et al.*, *Preliminary Legal Review of Proposed Medicines Patent Pool*, online: The Innovation Partnership <<http://www.theinnovationpartnership.org/data/documents/00000003-1.pdf>>.

31 IVB, *supra* note 14.

32 *Ibid.*

A final concern in the research environment is the increasing focus on commercialization by public sector research institutions that may undermine norms of open scientific collaboration, especially the sharing of research results and materials.<sup>33</sup> Increasing levels of industry funding may augment this effect and contribute to delays in the publication and dissemination of scientific research. There are real worries about the sharing of research materials and results in an increasingly competitive environment. The highly structured collaborations in the PPPs are partly designed to alleviate this problem, which stems, in part, from old fashioned competition between research groups for academic recognition and funding.<sup>34</sup>

Once vaccines are developed, exclusively held IP may restrict access to final products by developing countries as a result of expensive royalty fees or pricing strategies beyond public health budgets. This situation is well known with respect to developing countries and HIV/AIDS anti-retroviral drugs. Despite large numbers of infected individuals, there may be little money to be made from markets in the developing world. In these cases, the IP may simply not be developed by the exclusive licensor for those markets and developing country manufacturers are blocked from developing generic copies or accessing the IP to bring a product to their citizens. An organization known as the Developing Country Vaccine Manufacturers Network (DCVMN), which is a voluntary public health driven alliance of vaccine manufacturers from developing countries consisting of state-owned producers and private producers, indicated that an area of great concern to the group was the uncertainty or unknown elements of existing IPRs. For example, several patents already in place may impact them, including a broad patent on the use of the adjuvant aluminum phosphate in the manufacturing of combination vaccines.<sup>35</sup> Negotiating the patent landscape in

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33 Richard R. Nelson, "The Market Economy and the Scientific Commons" (2004) 33 *Research Policy* 455; Paul A. David, "Can 'Open Science' be protected from the evolving regime of IPR Protection?" (2004) 160 *Journal of Theoretical and Institutional Economics* 9.

34 John P. Walsh, Charlene Cho & Wesley M. Cohen, "View from the Bench: Patents and Material Transfers" (2005) 309 *Science* 2002.

35 See e.g. "Vaccine comprising aluminum adjuvants and histidine," U.S. Patent No. 7348006 (26 July 2002); see also "Adjuvant composition comprising aluminum phosphate and 3D-MPL", World Intellectual Property Organization (WIPO) Patent No. WO/2006/087563, (16 February, 2006).

vaccine production takes time, resources and expertise that this group may not have.<sup>36</sup>

Given this background it is crucial to understand how to use IP management strategies to aid innovation, and stimulate investment in HIV vaccine R&D while furthering the goal of ensuring affordable global access, particularly in developing countries. There are a number of sources one can look to find novel IP management strategies aimed at ensuring global access. These sources include national laws, where general IP strategies and goals are articulated. Of greater interest, however, are policies of government agencies involved in funding HIV vaccine research such as the U.S. National Institutes of Health (NIH), which may articulate more specific IP management terms. Organizations like the NIH can have a tremendous impact on research standards due to the sheer amount of funding they control. According to So, Rai & Cook-Deegan, "Through their grant agreements, public sector funders can influence how research institutions meet public health priorities or philanthropic objectives. Public sector funders include foundations as well as government research agencies, which can exercise non-funding leverage over these technology transfer norms."<sup>37</sup> In addition, IP strategies used in PPPs involved in vaccine development such as IAVI and, non-profit private organizations such as the Gates Foundation are creating new norms in vaccine IP management. We turn now to a discussion of such innovative IP strategies to ensure access to research tools for vaccine R&D.

## **Part Two: IP Strategies for Access to Research Tools**

The following discussion is on intellectual property and the problem of ensuring researcher access to necessary IP such that a research project is not "blocked" by third-party IP mid-stream. In this context we discuss: patent mapping, patent pooling, due diligence methods, provision of legal support services, and relationship building.

### **Access to Research Tools**

It is important to note that although patents on research tools can be problematic in some cases, IPRs are often not asserted at the research stage. This

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<sup>36</sup> IVB, *supra* note 14.

<sup>37</sup> Anthony D. So, Arti K. Rai & Robert M. Cook-Deegan, "Intellectual Property Rights and Technology Transfer: Enabling Access for Developing Countries" (2005) [unpublished, archived with author].

is a logical and practical response by the IP holders. Since the vast majority of HIV vaccine research candidates will be unsuccessful it makes little sense to seek injunctive relief at the earliest research stages and incur legal costs. So while there is ambiguity about the scope and nature of a research exemption in a number of countries including the United States and Canada,<sup>38</sup> this may not be as damaging in practice as it might initially appear. Given that

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38 The research or experimental use exemption curtails a patent holder rights by permitting researchers and research institutions to make certain uses of a patented invention without compensating the patent holder. Many policy documents argue that the research exemption for free-access to basic research materials should be strengthened. However, it is becoming increasingly difficult to justify a research exemption as the lines between private and public sector research blur and the commercialization activities of public sector research institutions increase. In the US, there is no statutory research exemption but, instead, a very narrow experimental use exemption that has been carved out by judges and exists in the common law. Previously the exemption did not apply if the research had “the slightest commercial implication”. However, the decision of the United States Court of Appeals for the Federal Circuit in *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002) [*Madey*] has further narrowed the exemption. Now any conduct by a research institution that is in keeping with its legitimate business, regardless of the commercial implications of the research, cannot rely on the research exemption. In the case of *Madey*, Duke University was using patented equipment for teaching and research. The court characterized both of these activities as part of the legitimate business activities of the university and therefore decided that Duke University could not be exempted from patent infringement. The result is that the research exemption has been restricted only to the most exceptional circumstances. In Europe, the issue of infringement is still largely determined by national patent law. Article 31 of the Community Patent Convention, or the EC, *Convention for the European Patent for the Common Market* [1976] O.J. L 17/43 [CPC], creates an exemption for acts “done for experimental purposes relating to the subject matter of the patented invention”. All members of the EU except Austria have introduced a similar provision into their national patent laws. However, the interpretation of the scope of the exemption still varies between countries. See Center for Intellectual Property Policy and Health Law Institute, *The Research or Experimental Use Exemption: A Comparative Analysis Report prepared for Health Canada* (CIPP & HLI, 2004), online: Center for Intellectual Property Policy <<http://www.cipp.mcgill.ca/data/newsletters/00000050.pdf>>; E. Richard Gold, Yann Joly & Timothy Caulfield, “Genetic Research Tools, the Research Exception and Open Science” (2005) 3:2 GenEdit 1.

industry practice tends towards non-assertion of patent rights for research use at initial stages this simplifies research projects at the initial stage but can lull researchers into a false sense of security. IPRs tend to be asserted when the prospect of a commercial application involving third-party IP develops.<sup>39</sup> This increases the importance of developing relationships and securing access to necessary research tools as early as possible, anticipating situations in which commercially viable products may result.

For many vaccine research projects, including HIV and malaria, adjuvants appear to be of utmost importance. And while proprietary adjuvants are generally available at the preclinical stage, the public sector needs to consider carefully investment in a promising candidate vaccine using a particular adjuvant. Public sector researchers and funders should ensure that there is documented industry commitment to make the adjuvant available for clinical development and commercialization. Where PPPs are involved, clear expectations and unambiguous contractual or licensing language is critical so that public sector goals are not thwarted.<sup>40</sup>

### *Creating a Patent Landscape*

One strategy for ensuring that HIV vaccine R&D is not blocked by downstream patents on IP is to create a patent landscape that clearly lays out the patents related to HIV vaccine R&D. This would include patents on antigens, adjuvants, vectors, purification methods, delivery methods, etc. Such an exercise enables researchers to identify where patents on research materials and tools exist and to determine whether access to the IP will be possible and affordable, where a work-around will be necessary or where the project will not be feasible.

Is it feasible to create a patent map for HIV vaccine patents? No partial or comprehensive HIV vaccine patent map exists to date. Compiling such a patent map would require the dedication of substantial financial and personnel resources.<sup>41</sup> Attempts to create such a map are frustrated by the sheer

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39 Personal communications with Louis C. Cullman, Partner, Kirkpatrick & Lockhart Preston Gates Ellis LLP and Erik Iverson, Associate General Council, Bill & Melinda Gates Foundation.

40 Joachim Oehler, "Using Milestones in Healthcare Product Licensing Deals to Assure Access in Developing Countries" in Anatole F. Krattiger *et al.*, eds., *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Oxford: MIHR, 2007) 119.

41 Lori Knowles completed an exhaustive literature review of scientific, medical,

volume (numbering in the tens of thousands) of potentially relevant patents and the difficulty of determining which HIV-related patents are relevant to vaccine development. Researchers at the Gates Foundation determined that collecting this information would be too expensive and require too great an investment in time. In addition, there are any numbers of patents on research tools and methods including patents on assays, adjuvants, vectors and methods that may impact HIV vaccine research but are not HIV-vaccine specific. Another factor frustrating such attempts is that much of the relevant IP pertaining to HIV vaccine R&D is held as proprietary trade secrets. This is particularly true as it relates to more downstream production and innovation. Conversations with officials at the AIDS Vaccine Advocacy Coalition (AVAC), the International AIDS Vaccine Initiative (IAVI) and the Center for HIV Vaccine Immunology (CHAVI) confirmed this conclusion. None of these groups has been able to compile a patent landscape for HIV vaccine R&D. It would be more cost and time effective to create project specific maps in conjunction with the due diligence techniques described below. An alternative is to create licensing maps in areas of specific global health innovations to determine where exclusive licenses may restrict freedom to operate.

### *Creating a patent pool*

Patent pools are another option for managing access to research tools for HIV Vaccine R&D. A patent pool is an arrangement in which “two or more patent owners agree to license certain of their patents to one another and/or third parties”.<sup>42</sup> Patent pools bring together patent holders in a spe-

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administrative and legal literature for discussion of major HIV vaccine patents. In addition, she conducted searches of public patent databases such as Freepatentsonline.com which yielded thousands of potentially relevant patents dealing with HIV related inventions although these did not indicate if they were relevant to HIV vaccine research in most cases. Knowles conducted interviews with personnel at AVAC, IAVI and the Gates Foundation to search for patent information. Patent mapping is theoretically possible but would require substantial financial and human resources (including experts in HIV vaccine research and vaccine development generally to read through the patent applications) and would likely take many months if not years. Tania Bubela developed a search algorithm based on keywords provided by Canadian vaccine researchers and found over 11,000 US patents in Delphion, a commercial search engine.

42 US Department of Justice and the Federal Trade Commission, *Antitrust Guidelines for the Licensing of Intellectual Property* (US Department of Justice and Federal

cific area of innovation, such as a viral genome, to facilitate the efficient use and development of a technology. The patents are “pooled” in the sense that the arrangement allows inventors in the pool to use all patented inventions under favorable licensing terms. Any benefits that may materialize are then shared among the group. Patent pools have been used successfully in the motion picture industry, in aeronautics and in the development of video and DVD technology.<sup>43</sup>

Patent pools can be helpful in streamlining the number of parties with whom licenses must be negotiated and in lowering costs associated with such negotiations. One way to create effective pools is to include a number of overlapping or necessary patents that together cover a recognized standard in the affected research. In other words, the patents cover an area generally recognized as essential to research in the area. The identification of the pooled patents as essential is generally necessary to avoid triggering anti trust or anti competition laws.<sup>44</sup> At this time there is no area of HIV vaccine research that describes an essential standard such that a pool of related patents could be created. In fact, biotechnology is characterized by the absence of such standards. A further problem occurs where there are no final products developed (as in HIV vaccines or SARS vaccines) it will naturally be more difficult to prove that any patent is essential. While proposals for an “upstream” SARS vaccine technology pool were floated in 2005, to date that pool has not been established.<sup>45</sup>

Two other obstacles stand in the way of establishing patent pools for biotechnological innovation in general and HIV vaccine development in particular. One study on patent pools in biotechnology concluded that patent

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Trade Commission, 1995), online: United States Department <<http://www.usdoj.gov/atr/public/guidelines/0558.htm>>; Ebersole *et al.*, *supra* note 29.

43 Jeanne Clarke *et al.*, *Patent Pools: A Solution to the Problem of Access in Biotechnology Patents?* (United States Patent and Trademark Office, 2000), online: United States Patent and Trademark Office <<http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>>.

44 Patrick Gaulé, “Towards Patent Pools in Biotechnology?” (2006) 2 *Innovation Strategy Today* 123.

45 Knowledge Ecology International, “IGWG Briefing Paper on Patent Pools: Collective Management of Intellectual property – the use of Patent Pools to expand access to essential medical technologies” (2007) 3 *KEI Research Notes* 1, online: Knowledge Economy International <[http://www.keionline.org/index.php?option=com\\_content&task=view&id=65&Itemid=44](http://www.keionline.org/index.php?option=com_content&task=view&id=65&Itemid=44)>.

pooling is generally not an effective tool in the area of vaccine research given the breadth and variety of different research projects.<sup>46</sup> In addition, the different nature of the IP owners – private and public sector – and their different priorities makes the creation of a pool more unlikely.<sup>47</sup> Despite this skepticism, in the future collaborative efforts like the CAVD may lead to the identification of some key platform patents related to a candidate vaccine with the result that pooling might be a useful strategy.

It might also be possible to create a pool of the most commonly used adjuvants in a particular vaccine research field. This is something under consideration at the Gates Foundation.<sup>48</sup> While there are hundreds of adjuvants patented for use in medical research, relatively few are widely used. Ensuring access to the necessary adjuvant is critical to the success of a research project. No adjuvant landscape mapping has been conducted to date for HIV

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46 See Anatole Krattiger *et al.*, “Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics: Case Studies on Pandemic Influenza, Malaria and SARS” (2006) 2 *Innovation Strategy Today* 67 (discusses barriers to patent pools in biotechnology and vaccine development, including anti-trust considerations, bargaining difficulties caused by asymmetric interests and asymmetric rights among IP holders (e.g., improvement vs. foundational patents), and the difficulties of securing financial support given the significant transaction costs associated with pools. They summarize the main concerns as follows at 68: “(1) Anti-trust considerations are real and may not be easily overcome in the quickly developing field of biotechnology. (2) Because they do not have aligned interests, it is doubtful that key players will agree to a patent pool. Without an industrially standardized suite of platform technologies, a situation that is unlikely to change in the near future, businesses compete at every level and have no reason to share their discoveries with their competitors. The best – known use of patent pools is in the electronics industry, which extracts value from IP through the finished product (e.g., DVD players sold to consumers). In biotechnology, however, value can be preserved and extracted at numerous levels of development. Moreover, the industry is made up of not only very large corporations but also very small start-ups. Their interests are usually opposed, which makes this field generally inimical to pool formation. (3) It would be a formidable obstacle to identify a donor willing to fund the significant cost of establishing a patent pool, especially in the area of limited commercial interest, such as products for the developing world.”

47 Gaulé, *supra* note 44; Krattiger *et al.*, *supra* note 46.

48 Personal communication with Erik Iverson, Associate General Council, Bill & Melinda Gates Foundation.

vaccine R&D, however, the MVI recently spent several months compiling a “data dump” of all the patented adjuvants related to vaccine research in general. From this information they propose to cull down to a list of those adjuvants that are actively being used, determine which ones hold promise for the MVI and then do some targeted IP mapping on those selected adjuvant targets. This is a long-term project, but one that might be relevant to funders of HIV vaccine R&D.<sup>49</sup>

Furthermore, in trying to avoid future patent thickets, funders can insert language into their grants that any IP resulting from a funded research project may be pooled with other funded research at a future time. Alternatively, language can be inserted into grant contracts that establish the obligation for grantee institutions to participate in pooling negotiations should the situation arise in the future.

An alternative to patent pooling that is particularly attractive where there are biotechnology patents is exclusive licenses to one party which aggregates all the complementary or overlapping patents. This can be helpful where the parties owning IP are academic institutions that lack the capacity to develop or produce the final product themselves. For example, the patents covering reverse genetics techniques required for pandemic influenza vaccine development were held by four parties, no one of which had production capacity. MedImmune, a vertically integrated biotechnology firm acquired control of the technology through exclusive licenses from all four parties and now provides a one-stop licensing authority for the technology.<sup>50</sup>

### *Pre-grant Due Diligence*

Given the difficulty of the science and the resulting wide variety of targets and techniques around which HIV vaccine research projects are designed, the experience of individual vaccine research projects with respect to relevant IP may not be relevant to other projects. This conclusion reached by a number of philanthropic foundations and PPPs necessitates case-by-case analyses of where IP, in the form of either patents or proprietary information, may hinder HIV vaccine R&D.

As a first step, every funder should require potential grantees to undertake a careful analysis of what background IP, materials and methods could

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49 Personal Communication with Dr. Donald Kelemen, Senior Commercialization Officer, Malaria Vaccine Initiative.

50 Gaulé, *supra* note 44.

be relevant to their research project including projections of what other IP might be needed if the research proceeds as planned. This description and forecasting forms the backbone to an approach referred to as the “due diligence approach.” The Gates Foundation originally assumed that individual grantees could map their own IP landscape; but that suggestion met with considerable push-back due to the time and resources it would take laboratory personnel to undertake such a study and the likelihood that such a study would not be complete due to the proprietary nature of some of the relevant IP. In mandating that grantees articulate an IP strategy, the Foundation will avoid situations where a research team simply relies on the existence of a “safe harbor” or research exemption. As discussed above, the existence of research exemptions is not clear, nor does it prevent IP blocks from arising when commercial applications from research become possible. Some researchers avoid delving into relevant IP information, daunted by the difficulty of accessing the information either due to a lack of legal knowledge and, more likely, the time it takes away from research. Provision of support in accessing this information will be a useful strategy. It makes sense to adopt the viewpoint that the creation of a project specific Global Access Strategy (which includes the IP management strategy), the due diligence process and the production of the necessary documentation are iterative processes.

The Gates Foundation has created documents detailing the key elements of preparing a Global Access Strategy with respect to the due diligence approach.<sup>51</sup> While a central piece of the due diligence approach is the IP management strategy, equal emphasis is placed on grantees having a business development team. In other words, the foundation wants to be certain that the organization is viable, and has in place the structure and mechanisms to manage the project, the consortium of researchers (if applicable), and the technologies and IP rights. Further due diligence ensures that anticipated post-project activities and issues such as further development and commercialization have been taken into account in structuring the project. Other experience indicates that backward-looking due diligence should be

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51 Personal communication with Erik Iverson, Associate General Council, Bill & Melinda Gates Foundation. As envisioned by the Bill & Melinda Gates Foundation, the key elements of preparing a Global Access Strategy include: Due Diligence for Technologies and IP Rights, Management and Product Maturation; Documentation for a Global Access Strategy; and Timing to Completion; recognizing that the most effective approach to completing a Global Access Strategy is an iterative one with the Foundation.

conducted to sort out complications from pre-grant arrangements with previous sponsors or partners regarding IP that might hinder the realization of the Global Access Strategy.

IAVI and the EDCTP also follow a due diligence approach in structuring their relationships with grantees and/or partners. EDCTP described their process as follows:

Before the start of a project all IP-rights concerned shall be identified, including all obligations already contracted by third parties. The EDCTP shall endeavor to assess whether the actual IP-rights position might prevent the project from ultimately resulting in an affordable intervention for developing countries. During the execution of a project the EDCTP shall assist the research sites with legal matters concerning IP-rights wherever necessary.<sup>52</sup>

In conclusion, those investing in HIV vaccine R&D, whether governments, private sector, or PPPs, should consider focusing some resources on funding project-specific patent mapping with the assistance of the grantee researchers. This would involve mapping the patents in the research territory in which the researchers are working. Such a search would be broader than IP due diligence but narrower than an entire patent map. The time needed and resources required could be significant and will vary depending on the individual research project.

In addition, legal support services should be provided to grantees. Some PPPs and grant-makers provide legal support to sponsored research teams, technology transfer offices or organizational legal counsel. This legal support can take the form of help understanding contractual obligations; help navigating an IP problem; negotiating with IP holders; drafting licensing terms; attaining commitments from IP holders that they will not assert (litigate for patent infringement) their patent rights; providing expertise in drafting patent applications; and, providing financial and legal support with patent filings.

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52 European and Developing Countries Clinical Trials Partnership (EDCTP), *Guideline on Intellectual Property Rights*, online: EDCTP <[http://www.edctp.org/fileadmin/documents/Guideline\\_IP.pdf](http://www.edctp.org/fileadmin/documents/Guideline_IP.pdf) >.

### *Engaging in Relationship Building*

Surprisingly, one of the best pieces of advice for IP management concerns choosing the right research projects for funding. The model for HIV vaccine research is increasingly collaborative; there is consensus that an HIV vaccine will not be developed in isolation, but through some sort of collaborative effort.<sup>53</sup> The “right” projects therefore, are those with the greatest scientific merit from teams with a proven track record and the necessary infrastructure to set the stage for project success, *and* teams that are composed of individuals who are easy to work with and good communicators. This seems trite, but case studies continually show that the crux of a successful project is a shared common vision and purpose among stakeholders and the development of excellent partnership relationships based on respect and trust. This is essential for projects structured as collaborations or as PPPs, but equally important for individual academic researchers who will likely need to work with partners or negotiate with IP holders at some point. Written contractual obligations<sup>54</sup> are no substitute for excellent partnering relationships<sup>55</sup>, although both are necessary to meet global access goals.

### *Create networking and educational opportunities for Academic IP managers*

There are very few technology transfer managers who have experience in managing global health technology.<sup>56</sup> A greater awareness of issues and new opportunities related to global health technology management can be facilitated by providing multidisciplinary training and by helping to forge professional relationships with IP managers from other sectors.<sup>57</sup> In vaccine development, partnerships between university researchers and PPPs are fundamental to bringing vaccine candidates and related technologies to development. Facilitating the formation of these relationships through face to face networking and educational meetings is an excellent use of resources. Such meetings provide technology transfer managers and researchers from

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53 Personal communications with Louis C. Cullman, Partner, Kirkpatrick & Lockhart Preston Gates Ellis LLP.

54 IVB, *supra* note 14.

55 Oehler, *Supra* note 40.

56 Usha Balackrishnan, Lisa Troyer, Edwin Brands, “Surveying the Need for Technology Management for Global Health Training Programmes” (2006) 18 AUTM Journal 53.

57 *Ibid.*

major universities, counterparts in relevant companies, and staff from PPPs with a chance to meet in order to learn and understand their shared research goals and interests. These meetings facilitate future working relationships and negotiations as well as providing opportunities to identify synergistic activities.

In conclusion, a plethora of widely held IP in vaccine research may impede HIV vaccine R&D, especially as it approaches commercial application. There are a number of solutions, some more complex than others. A full patent landscape for HIV vaccine R&D is unfeasible and the creation of a patent pool is likewise, a complex alternative that has seen limited success in biotechnological applications. Simpler short-term solutions include project specific due diligence methods to ensure that specific projects do not infringe IP, the provision of legal support services in negotiating with patent holders, the support of funding agencies, and policies that facilitate collaboration and the sharing of IP, particularly for publicly funded research. Finally, the importance of relationship building in the HIV vaccine research community cannot be underestimated. We now turn from a discussion of potential IP blockages for HIV vaccine R&D to a discussion of IP in the context of access to the innovative products and processes resulting from vaccine R&D.

### **Part 3: Global Access Strategies**

In this section, we address the issue of ensuring global access to any products of funded research, be they research tools or more downstream products including actual vaccines. In this context the discussion focuses on contractual IP management and creative licensing strategies a Global Access Strategy.

A pressing concern for those involved in HIV vaccine research is ensuring that research products, be they upstream research tools or ultimately downstream HIV vaccine candidates, are accessible to the widest extent possible. Special efforts must be focused on ensuring the benefits from publicly-funded research projects benefit middle and low income countries that are disproportionately affected by HIV-AIDS. The first point to keep in mind is that a number of IP management strategies which may be very effective in some situations will be inappropriate or impossible in others. This is well articulated by the authors responsible for proposing equitable access licenses:

One of the lessons of our analysis of various licensing provisions is that there is no one-size-fits-all commons-based strategy. Different strategies to create and sustain commons-based production in different contexts may be required by: different economic characteristics of research areas; different industrial structures and relative roles of

market-based, governmental, and nonprofit enterprises; and different types of exclusive rights regimes.<sup>58</sup>

There are, however, some generalizable strategies that can be followed. These include the clear articulation of common goals concerning the promotion of global access and IP management.<sup>59</sup>

### *Outlining Grantee Obligations*

Articulation of project or collaboration goals from the beginning ensures that a shared understanding of the mission and outcomes of the project exists between diverse parties and between the grantee and the grantor. An upfront agreement should also articulate the management of IPRs associated with project inventions. For example, as a general principle, universities, governments and non-profits might agree that research tools should be made as widely available as possible. More specific IP management strategies might include identifying methods to secure, manage and allocate IPRs, and the framework by which the grantee and project collaborators will own, manage and license the related IP rights.

Grantors may also wish to include a provision for certain IP events to trigger reporting requirements. For example, before a decision about filing a patent application or licensing terms is made, a grantor may require the grantee to report to the grantor and/or other collaborators so that the implications for the Global Access Strategy can be thoroughly reviewed. In addition, more tangible methods for allowing access within a partnership or collaboration, or even a research community should be described. This might include dissemination strategies that concern how and when to publish research findings, or more contractual requirements for materials and data sharing. Ultimately the most important feature of a Global Access Strat-

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58 Amy Kapczynski *et al.*, "Addressing Global Health Inequities: An Open Licensing Approach for University Innovations" (2005) 20 Berk. Tech. L. J. 1031 at 1041.

59 Personal communication with Erik Iverson, Associate General Council, Bell & Melinda Gates Foundation. A Global Access Strategy should, at the outset, identify material background technologies and those anticipated during the project; describe strategies to secure, manage and allocate IPRs associated with project inventions; describe reporting of IP events to stakeholders; describe the reporting of results; anticipate post-project activities; and identify commitments made to support the furthering of Global Access objectives.

egy is to think through the specific management of IP that might be needed or flow from the project and to ensure that all parties understand and have clear expectations about their moral and contractual obligations, throughout the life of the project and even beyond.

Global Access Strategies must be visionary to incorporate possible but uncertain events. To that end they can include provisions for continued responsibilities beyond the project timeframe. To a certain extent requiring researchers to envisage post-project activities helps to ensure the global access objectives are met. It is a method to assure that project leaders have a real implementation plan and have given some thought as to potential obstacles, specifically, how research results will be incorporated into other products or services and how researchers might respond to the needs of the developing world.

### *Creative Licensing Strategies*

There are a number of creative licensing strategies used by both public sector and PPP groups to ensure that the benefits of health biotechnology reaches the people in low and middle income (LMI) countries. Humanitarian licensing strategies focus on avoiding future IP obstacles with the goal of ensuring people in the developing world get access to essential medicines. These strategies create licensing arrangements that facilitate the translation of research projects from the laboratory through product development while ensuring that the products of that research are transferred to the developing world in an affordable and timely manner. Humanitarian licensing is relatively new; its success is still unknown although there are a few successful case studies.<sup>60</sup> The success of humanitarian licensing depends to a great extent on the willingness of private sector actors to accept licensing conditions that increase access later in a project's development and marketing stages. As unlikely as this may sound, for many private sector parties there is

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60 For example the story of Artemisin, a traditional herbal remedy in Chinese medicine, has proven value as an antimalarial, particularly in combination with other drugs. A research team at University of California, Berkeley developed a process to produce artemisinic acid and Amyris Biotechnologies developed a production process for artemisin. Backed by a \$42.6 million grant from the Bill & Melinda Gates Foundation, the Institute for OneWorld Health forged a non-profit partnership with UC Berkeley and Amyris Biotechnologies. OneWorld Health and Amyris entered into an exclusive development and commercialization agreement, and Amyris committed to taking "no profit from the sales of this product to the developing world" *So et al., supra* note 37.

little profit foregone in developing country markets and there is great public goodwill to be gained.<sup>61</sup>

University charters have a clear public purpose; academic technology transfer offices (TTO) therefore, also serve that public purpose by ensuring that inventions created at the university benefit the public through appropriate dissemination. A recent statement by a collection of US Universities is worth reproducing:

Around the world millions of people are suffering and dying from preventable or curable diseases. The failure to prevent or treat disease has many causes. We have a responsibility to try to alleviate it, including finding a way to share the fruits of what we learn globally, at sustainable and affordable prices, for the benefit of the world's poor. There is an increased awareness that responsible licensing include consideration of the needs of people in developing countries and members of other underserved populations.

The details involved in any agreement provisions attempting to address this issue are complex and will require expert planning and careful negotiation. The application will vary in different contexts. The principle, however, is simple. Universities should strive to construct licensing arrangements in ways that ensure that these underprivileged populations have low- or no-cost access to adequate quantities of these medical innovations.<sup>62</sup>

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61 Amanda L. Brewster, Audrey R. Chapman & Stephen A. Hansen, "Facilitating Humanitarian Access to Pharmaceutical and Agricultural Innovation" (2005) 1 *Innovation Strategy Today* 203.

62 Arthur Bienenstock et al., *In the Public Interest: Nine Points to Consider in Licensing University Technology* (6 March 2007), online: Stanford University <<http://news-service.stanford.edu/news/2007/march7/gifs/whitepaper.pdf>>. The main principles put forward by this group of universities include:

- Universities should reserve the right to practice licensed inventions and to allow other non-profit and governmental organizations to do so,
- Exclusive licenses should be structured in a manner that encourages technology development and use,
- Ensure broad access to research tools, and
- Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.

It has become clear that ensuring that appropriate dissemination reaches the developing world will require some innovations in licensing the technology from academic technology transfer offices (TTOs) to the private sector. Most humanitarian licensing strategies are employed by universities when licensing IP to PPPs or to the private sector. These strategies can also be used by private philanthropy and by government funding agencies. Although the National Institutes of Health (NIH) in the United States does engage in humanitarian licensing, it has its own guidelines and policies, discussed below.

The central characteristic of humanitarian licensing is the avoidance of granting worldwide exclusive licenses without reservations. This is an approach shared by the NIH. Generally humanitarian licensing will employ non-exclusive licenses that use various types of market segmentation to permit the private sector to recoup its investment while serving the needs of LMI countries. These licenses can be structured any number of ways. For example:

1. The licensor can give an exclusive license to a commercial company limited to development of a vaccine or medicine in the developed world while retaining the freedom (a reserved right) to license the technology to other parties, such as nonprofit PDPs, who will develop and market the technology for LMI countries. Negotiating with the non-profit partner prior to formalizing a licensing agreement with a commercial partner can lower the transaction costs to the non-profit licensee when segmenting the market between developed and developing countries.
2. Licensors can license technology for LMI country development at significantly reduced royalties or can donate the technology or know-how to non-profits for the same purposes or licensors can structure licensing agreements requiring a commercial licensee to provide know-how to LMI countries.
3. TTOs and other public sector licensors can seek commercial partners in LMI countries to develop technologies that address conditions specific to those regions. Such partners may be able to develop, produce, and distribute the product at much lower cost than typical partners in developed countries.
4. The licensor can structure a license such that the licensee may first introduce a product in the developed world but thereafter has obligations to introduce the product to developing countries. These

obligations can be structured around benchmarks or milestones as discussed below.

5. Universities can reserve for themselves and for other universities or non-profits the right to use the technology or materials for research purposes. TTOs can also use simplified material transfer agreements (MTA) and data sharing agreements to facilitate the transfer of materials between research institutions. The NIH and the Gates Foundation have created model language for simplified MTAs to facilitate such agreements.
6. The licensor can structure the license such that the technology is to be subject to differential pricing such that the licensee recoups its investment on the developed world product but must make the technology available at appropriately lower prices to LMI countries. This preferential pricing for LMI countries requires a shared understanding of what “reasonable pricing” means to both licensor and licensee. To ensure that an appropriate price is reached and maintained, the licensor may also include contractual language that mandates the submission of manufacturing cost reports and project cost calculations on a regular basis.<sup>63</sup>
7. Licensors might mandate that pricing of technologies in LMI markets be based on a cost-plus basis rather than the retrograde calculation used by pharmaceutical companies which includes significant recuperation for the high marketing costs incurred by these companies. Public sector cost-plus pricing methods include a small profit on manufacturing and production costs.<sup>64</sup>

A more radical model of licensing based on an open commons model is the Equitable Access Licenses (EAL) proposed by Universities Allied for Essential Medicines.<sup>65</sup> This model seeks to introduce a freedom to operate model for generic production and distribution of any medicine in LMI countries. This method has not yet been adopted and might not be feasible for biologicals

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63 Kapczynski, *et al.*, *supra* note 58.

64 Oehler, *supra* note 40.

65 Universities Allied for Essential Medicines (UAEM), *Modern Provisions for an Equitable Access and Neglected Disease License* online: UAEM <<http://www.essentialmedicine.org/EAL.pdf>>.

such as vaccines given their complexity and the critical role of know-how transfer as noted by the authors themselves.<sup>66</sup>

One challenge in structuring licensing agreements with segmented markets is to clearly define the beneficiaries. Defining the population or identifying the institutions that could serve this population avoids future conflicts. Various lists including the LMI countries listed by the World Bank or FAO or the OECD or the least developed countries list by the UN can be useful. Parties can decide whether middle income countries are to be included or not. Another situation in which definitions need to be clear is where there are geographical limitations in a license agreement.

### *Milestones in licensing agreements*

Milestones are used in contractual agreements to ensure parties live up to specified obligations. They may be delivery milestones structured around dates for delivery of a product, geographical limitations (related to market segmentation or product introduction), or performance requirements. Clearly defined milestones in a licensing agreement require a licensee to fulfill an obligation under the agreement. Such milestones can be powerful incentives to induce private sector companies to address obligations to developing countries that, lacking a market incentive, might not be realized or not realized in a timely fashion. Public sector licensors, PPPs, governments and private foundations are relying increasingly on performance milestones to ensure public benefit flows from their IP. It is typical to keep a right of reversion that is triggered if an obligation or milestone is not met. A penalty for non-performance could be loss of exclusivity, forced sublicensing, exercise of a “march-in” right such as that specified by the NIH, or even termination of the agreement. Clearly, milestones have to be agreed upon. They must be very clearly articulated and there must be penalties along with rights to cure the lapse. So for example, where negotiation milestones refer to the introduction of a product into LMIs, it is necessary for the parties to agree on what definition of LMI they want to use.<sup>67</sup> There is also need for flexibility in revising milestones as a project progresses.<sup>68</sup>

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66 Kapczynski, *et al.*, *supra* note 58 at 1095.

67 Personal communication with Steven Ferguson, Office of Technology Transfer, National Institutes of Health.

68 Oehler, *supra* note 40.

## Governments: Administrative Solutions

National laws can articulate a government's commitment to certain larger ideals for the use of IP protection such as benefiting the public or promoting public health. Some laws will be important for the effect they have on IP management in certain sectors such as academia. Where statutes articulate IP management strategies, they articulate long-term solutions rather than quickly addressing the problems at hand. Government agencies and PPPs may also use contracts examined in the context of national laws, primarily those of the United States and the European Union.

### *The United States*

In 1980 two important IP-related laws were passed that constitute the statutory and administrative framework governing the dissemination of research conducted or funded by the U.S. federal government. The *Bayh-Dole Act* enabled university researchers to patent and license inventions created with federal funds thereby transferring technology into the private sector.<sup>69</sup> A similar law, the *Stevenson-Wydler Act*, enabled federal laboratories to patent inventions created with federal money as well.<sup>70</sup> These acts set out the framework for using Cooperative Research and Development Agreements (CRADA) with the NIH. These laws have been credited with catalyzing the growth of the US biotechnology industry but have also been blamed for increasing secrecy in American universities and stifling the free exchange of scientific ideas and discoveries.<sup>71</sup>

While *Bayh-Dole* gives federal grantees significant independence in crafting licensing policies, the act recognizes that these licensing policies might not always further the NIH's goal of promoting the public welfare through access to federally funded products and inventions. Thus the act gives the NIH "march-in" rights, specifically, the NIH has the authority to compel licensing if the patent holder (university) or exclusive licensee is not exploiting licensing rights in a manner that brings the NIH-funded research to the public. While the threat of march-in rights may be an effective tool in principle, march-in rights have never been used to make medicine more accessible

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69 *Bayh-Dole Act*, Title 35 U.S.C. 200 *et seq.*

70 *Stevenson-Wydler Technology Innovation Act of 1980*, Pub. L. No. 96-480, 94 Stat. 2311.

71 Heller & Eisenberg, *supra* note 27; Walsh *et al.*, *supra* note 34.

due to constraints the act puts on implementation and on the NIH's narrow interpretation of the scope of the power.<sup>72</sup>

In response to *Bayh-Dole Act*, US universities have opened TTOs and there has been a surge in university patenting. Despite the increased patenting activity, which is reinforced by government granting agencies looking at number of patents as a measure of productivity, TTOs generally do not make money.<sup>73</sup> Other than a few outliers, patent royalties compared to total university revenue constitute about 0.5 to 2% of revenues.<sup>74</sup> There is, in fact, a slow pendulum swing back from the rampant patenting of research tools and exclusive licensing of university inventions and there are even a few examples of innovative arrangements with developing country partners.<sup>75</sup>

An interesting initiative in the US legislature took place in 2007; (senate bill) S. 569 short title *Vaccines of the Future Act, 2007* was introduced on February 13, 2007 by Senator Richard Lugar (R-IN).<sup>76</sup> A companion bill, H.R. 1391 was introduced by the House of Representatives March 7, 2007 by Senator Visclosky (D-X).<sup>77</sup> The purpose of the senate Bill is "to accelerate efforts to develop vaccines for diseases primarily affecting developing countries." The Bills acknowledge that because the developing country market is small and unpredictable, there is insufficient private sector investment in research for vaccines for neglected diseases (defined to include HIV/AIDS).

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72 Arti Rai & Rebecca Eisenberg, "Bayh-Dole Reform and the Progress of Biomedicine" (2003) 66: 1&2 Law & Contemp. Probs. 289.

73 For example, see the results of AUTM licensing surveys (Association of University Technology Managers (AUTM), "Licensing Surveys", online: AUTM <[http://www.autm.net/about/dsp.licensing\\_surveys.cfm](http://www.autm.net/about/dsp.licensing_surveys.cfm)>).

74 Kapczynski, *et al.*, *supra* note 58 at 1088.

75 For example, University of California, Berkeley has an agreement with the island of Samoa for the development of the new AIDS and cancer drug, prostatin, derived from native uses of the mamala tree. The agreement allows for benefit sharing with Samoa and various villages and the University has committed to "exert reasonable efforts in licensing such patents or copyrights for public benefit, keeping in mind UC Berkeley's and Samoa's mutual goals of providing low cost therapies for free, at cost, or with minimal profit in the developing world." So, *et al.*, *supra* note 37.

76 U.S., Bill S. 569, *Vaccines for the Future Act of 2007*, 110<sup>th</sup> Cong., 2007, online: GovTrack.us <<http://www.govtrack.us/congress/bill.xpd?bill=s110-569>>.

77 U.S., Bill H.R. 1391, *Vaccines for the Future Act of 2007*, 110<sup>th</sup> Cong., 2007, online: GovTrack.us <<http://www.govtrack.us/congress/bill.xpd?bill=h110-1391>>.

Consequently the Bill mandates the creation of “a broad range of economic incentives to increase private sector research on neglected diseases”, an action deemed critical for the development of vaccines for neglected diseases. Other significant terms of the bill call on the President of the United States to support the GHAVE and to work with others in the international community to address obstacles to the development of vaccines for neglected diseases including but not limited to IPRs. Finally the Bill calls for the promotion of PPPs as a central element in the strategy to create effective incentives for vaccine development; the creation of comprehensive strategies to accelerate efforts to develop vaccines for neglected diseases, such as strategy to “address IP issues”; and authorises the Secretary of the Treasury to negotiate the participation of the United States in the advance market commitments of the GAVI alliance. While the Bill was referred to Committee and did not emerge, it signals at least some political awareness and desire to move in the right direction.

### *NIH Policy and Guidelines*

When universities began patenting NIH-funded research products, open sharing of research tools (tools scientists use in the laboratory, such as targets and tools for scientific discovery including monoclonal antibodies, receptors, animal models, libraries, computer software and databases) was constrained.<sup>78</sup> In partial response, in 1999 the NIH announced its new *Principles and guidelines for recipients of NIH research grants and contracts on obtaining and disseminating biomedical research resources: final notice* for the sharing of research resources developed with NIH funding.<sup>79</sup> The policy is articulated in two parts: principles, setting forth fundamental concepts; and guidelines, providing specific information, strategies and model language to scientists, patent and license professionals and sponsored research administrators.<sup>80</sup>

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78 Steve M. Ferguson & J.P. Kim, “Distribution and licensing of drug discovery tools – NIH perspectives” (2002) 7 *Drug Discovery Today* 1102.

79 National Institutes of Health, Department of Health and Human Services, “Principles and guidelines for recipients of NIH research grants and contracts on obtaining and disseminating biomedical research resources: final notice” (1999) 64:246 *Federal Register Notice 72090*, online: National Institute of Health <[http://www.ott.nih.gov/policy/rt\\_guide\\_final.html](http://www.ott.nih.gov/policy/rt_guide_final.html)>.

80 Ferguson & Kim, *supra* note 78.

The fundamental principles behind the *Principles and guidelines* include:

1. *Ensuring academic freedom and publication*: Recipients of NIH funding are expected to avoid signing agreements that unduly limit the freedom of investigators to collaborate and publish. This includes avoidance of unreasonable delays in publishing research results (while brief delays for patent filings are deemed reasonable).
2. *Appropriate implementation of the Bayh-Dole Act*: Restrictive licensing practices should be avoided. While *Bayh-Dole* encourages transfer of federally-funded research results to the public through commercialization, where the invention is primarily useful as a research tool, exclusive licensing may not be appropriate. If further R&D and private sector investment are required to realize the utility of a research tool invention then an exclusive license may be appropriate. If this is not the case, licensors should use other strategies to meet the goals of *Bayh-Dole* including “publication, deposit in an appropriate databank or repository, widespread non-exclusive licensing, or any other number of dissemination techniques.”<sup>81</sup> Licenses should be carefully crafted to fit individual case circumstances while ensuring widespread and appropriate distribution of research tools. In general, therefore, non-exclusive licensing is favored by NIH. When an exclusive license is necessary to promote investment in commercial applications of a subject invention the licensor should ordinarily limit the exclusive license to the commercial field of use, retaining rights regarding use and distribution as a research tool.<sup>82</sup>

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81 *Ibid.*

82 National Institutes of Health, Department of Health and Human Services, *supra* note 78 at 72095 (examples of possible language include: “‘Research License’ means a nontransferable, nonexclusive license to make and to use the Licensed Products or Licensed Processes as defined by the Licensed Patent Rights for purposes of research and not for purposes of commercial manufacture, distribution, or provision of services, or in lieu of purchase, or for developing a directly related secondary product that can be sold. Licensor reserves the right to grant such nonexclusive Research Licenses directly or to require Licensee to grant nonexclusive Research Licenses on reasonable terms. The purpose of this Research License is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however,

3. *Minimize administrative impediments to research:* Transfer of materials between academic institutions should be swift and use model MTAs. NIH recommends reliance on the use of the *Simple Letter Agreement of the UBMTA* for transfer of non-patented research materials. Universities should develop clear policies and model agreements that allow swift dissemination of federally-funded research tools. Licensing agreements for research tools or upstream innovations that require payments of royalties when a downstream commercial product is developed with their use (referred to as “reach-through” royalties) are to be discouraged.<sup>83</sup>
4. *Ensure dissemination of research resources developed with NIH funds:* NIH-funded recipients are expected to manage their interactions with for profit third-parties, including research sponsors (such as biotechnology or pharmaceutical companies) to avoid restrictions that might constrain further research. NIH principles should be shared with third-party sponsors. In addition, NIH supports funding recipients making a distinction between sharing research tools with for profit institutions for internal use and sharing them for commercial development. In the former situation policies should be developed that facilitate swift transfer and funding recipients should not seek royalties or option rights on final products.<sup>84</sup>

#### *NIH vaccine licensing strategy*<sup>85</sup>

With respect to neglected diseases and vaccines, NIH has adopted a strategy of ensuring its goal of improving public health is fulfilled by using “white knight” clauses, benchmarks with licensees, and engaging in regional licensing. In exchange for a “worldwide” license the NIH may insert some humanitarian type provisions into a licensing agreement. These “white knight”

Licensors shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of the materials”).

83 National Institutes of Health, Department of Health and Human Services, “Use of Simple Letter Agreement” online: NIH <[http://ott.od.nih.gov/policy/rt\\_guide\\_final.html#3](http://ott.od.nih.gov/policy/rt_guide_final.html#3)>.

84 Steven M. Ferguson, “Products, Partners & Public Health: Transfer of Biomedical Technologies from the U.S. Government” (2002) 5:2 J. BioLaw & Bus. 35.

85 Lori Knowles is grateful to Steven Ferguson of the NIH for sharing his knowledge of NIH vaccine licensing strategies.

clauses may include conditions requiring the licensee to do specific good things to benefit disadvantaged populations. These obligations might include marketing a product in developing nations at a reduced royalty or price, donating materials for clinical trials, mandating the supply back of licensed products or services or adopting reduced royalties for developing countries. NIH also requires licensees to create a world wide development and marketing plan to facilitate developing country access to licensed products, the implementation of which it monitors through agreed upon milestones.

The NIH requires a strategic plan for development of developing country deployment after the product launch has taken place in the developed world market. While this gives the licensee the opportunity to determine the profit that may be associated with the vaccine, it does mean a delay of 6-8 years between product launch and readiness for launch in the developing world. As of now, no licensee has provided an inadequate plan such that the NIH has had to exercise any type of reversionary interest (march-in rights).

In addition to white knight clauses and global access benchmarking, the NIH is following a strategy of regional licensing for vaccines that might not have acceptable risk ratios for the developed world but do for the developing world. The best example for this is the RotaShield vaccine for rotavirus, which was pulled from global circulation in 1999 by Wyeth-Ayerts Labs, the holder of the exclusive license, following the reporting of a small number of cases of intestinal blockage.<sup>86</sup> While the risk-benefit ratios might not have been acceptable for the developed world, the risk was acceptable for the developing world where more than 130 million episodes of diarrhea and 600,000 deaths occur annually.<sup>87</sup> In fact, subsequent data showed that the rate of intestinal blockage was acceptable for developed world standards.<sup>88</sup> However, the option of producing the vaccine for the developing world was contingent on the developed world market. Had the NIH held rights of reversion for non-performance they might have been able to sublicense the developing world market, but they did not. Finally in 2002, GAVI dedicated \$30 million to the introduction of a rotavirus vaccine into developing coun-

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86 The rate was one additional case of intestinal blockage than expected per 10,000 children vaccinated.

87 So *et al.*, *supra* note 37.

88 *Ibid.*: A reappraisal of the data later placed the risk at 1 excess case per 32,000 vaccinated infants between 45 and 210 days old, the target population for the vaccine. In the first year of life, the background rate of intestinal blockage in the United States is 1 case per 3,000 infants.

tries. In 2004, the National Institute for Allergy and Infectious Diseases, the original developer of the oral rotavirus vaccine, signed a new license agreement with BIOVIRx, which plans global commercialization of the vaccine. The vaccine has now been licensed regionally to countries with manufacturing capacity such as Brazil, China and India.

### *European IP Strategies*

Despite some of the negative effects of *Bayh-Dole*, the Act is often credited with the growth of the biotechnology sector in the U.S. This has led many countries<sup>89</sup> to adopt policy initiatives for shifting ownership of publicly-funded inventions from government or the funding agency to the entity performing the research.<sup>90</sup>

In Europe, some regulations focus on tiered pricing and trade diversion which are relevant to HIV vaccine production. The EU established a global tiered pricing system for key pharmaceuticals for the prevention, diagnosis and treatment of HIV/AIDS. Following this the European Council passed regulation No 953/2003 of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines.<sup>91</sup> This regulation establishes a procedure for manufacturers to apply for tiered pricing of medicines, including vaccines (preventative medicines) for HIV/AIDS, malaria, TB and other related opportunistic diseases. In this way, the poorest developing countries are supplied with essential pharmaceutical products at heavily reduced prices but lower priced medicines are prevented from being diverted to the EU for reselling.<sup>92</sup>

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89 Countries where some sort of shift like this is occurring include Australia, Britain, Canada, France, Germany, Sweden, Italy and Japan, *So, et al., supra* note 37.

90 Along with individual national searches, searches of the European Research Council and the European Heads of Research Councils (EUROHORC) were also conducted as well as searches on EU research databases.

91 EC, *Commission Regulation (EC) 953/2003 of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines*, [2003] O.J. L 135/5.

92 For example, it mandates that reduced priced products have a different appearance for easy identification.

### *European and Developing Countries Clinical Trials Partnership (EDCTP)*

The EDCTP aims to develop new clinical interventions to combat HIV/AIDS, malaria and tuberculosis through a long-term partnership between Europe and developing countries.<sup>93</sup> The EDCTP is a partnership between 14 EU countries, Switzerland and Norway and several African countries. It aims to join relevant European national research programmes with African partners to develop new clinical tools against AIDS, malaria and tuberculosis. There is only one clinical trial on a potential HIV vaccine funded by a national programme at this time. There are few, if any, current research sites in Africa with the capacity, either in knowledge of epidemiology or in the laboratory, for Phase III studies of HIV vaccines. For these reasons developing and co-coordinating this capacity will be an initial priority for the EDCTP.

### *EDCTP Guideline on Intellectual Property Rights*

One of the aims of the EDCTP is to ensure that the projects funded will benefit the people in developing countries, therefore, funding from the EDCTP is conditional on the formulation of IPR provisions that endeavor to ensure “people of developing countries have easy and affordable access to the research results produced by activities under the EDCTP Programme and to the products directly deriving from its results.”<sup>94</sup> Beyond this threshold statement the EDCTP IP policy states that a “general policy will be difficult to define that is applicable to the various combinations of potential partners. Thus, the specific IP-rights issues should be addressed on a project-by-project basis.”<sup>95</sup> Nonetheless the EDCTP states that it will develop a policy on IP management that addresses issues of knowledge ownership, and tiered pricing agreements with provisions on timing and pricing to inform governments.

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93 EC, *Commission Decision (EC) 1209/2003/EC of the European Parliament and of the Council of 16 June 2003 on Community participation in a research and development programme aimed at developing new clinical interventions to combat HIV/AIDS, malaria and tuberculosis through a long-term partnership between Europe and developing countries, undertaken by several Member States*, [2003] O.J. L 169/1. The decision also called for the “formulation of the provisions relating to [IPRs] in such a way that they also aim at ensuring that the people of developing countries have easy and affordable access to the research results produced by activities under the EDCTP Programme and to the products directly deriving from its results” at 3.

94 EDCTP, *supra* note 52 at para. 1.

95 *Ibid.*

EDCTP grantees must develop dissemination timelines and ensure that knowledge generated by funded projects including results of trials enters the public domain in a timely fashion. EDCTP retains the right to publish research results should a grantee fail to do so. The EDCTP, "while accepting in principle the need for strong IPRs protection in developed countries, will not seek in general IPRs protection in developing countries."<sup>96</sup> In addition, the EDCTP adopts a due diligence approach described above.

With respect to licensing to third parties, the basic principle is that the EDCTP will favor the transfer of IPRs if it will facilitate availability of affordable medicines to the people in developing countries. Grantees must share the principles of the EDCTP with third parties and obtain guarantees to meet these principles.

The EDCTP will not hold IP itself although it may retain some IP rights to ensure that its objectives with respect to developing country access are met. Interestingly, IAVI and the Gates Foundation originally also chose not to hold any IP themselves. IAVI, however, indicated in a WHO workshop that it found simply getting access commitments to necessary IP was not sufficient and that owning IP gave them much greater control through the licensing process.<sup>97</sup> The Gates Foundation continues not to own IP themselves, although they might consider doing so in the future.<sup>98</sup>

## Conclusion: Summary of Strategies

To encourage HIV vaccine research, government funders should carefully select research teams based on past performance, ability to work collaboratively and infrastructure. Excellent researchers who also possess the personal skills to work with other teams and to develop relationships with holders of IP with whom they will need to negotiate licensing terms are a valuable asset to a R&D partnership.

The PPP has proven itself to be the most effective model for HIV vaccine R&D because it leverages the expertise of the public sector in basic research and that of the private sector in product development. Most governments and PPPs assume that IP protection is crucial for private sector partners investing in health-related technologies with significant developing country

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<sup>96</sup> *Ibid.* at para. 3.

<sup>97</sup> IVB, *supra* note 14.

<sup>98</sup> Personal communication with Erik Iverson, Associate General Council, Bill & Melinda Gates Foundation.

markets.<sup>99</sup> Since dual markets exist (developed and developing markets) for HIV vaccines, incentives for *initial* market development are not generally a problem as patents may provide the incentive to develop a developed country product.<sup>100</sup> However, given the significant developed country market segment for an HIV vaccine, market segmentation strategies should be part of an IP management strategy. Such a strategy will ensure corporate investment and timely development and appropriate pricing for developing countries.

An initial strategy when bringing together a research team or several members of a collaborative effort or establishing a PPP should be the articulation of general IP management principles for a global access strategy. All members of the team or collaboration should share these general principles. This step helps ensure common goals and guides grantees and partners in their R&D interactions and any subsequent licensing decisions or negotiations. IP management strategies are one component of global access strategies that may include know-how transfer, capacity building in developing countries, pricing strategies such as tiered pricing, anti-diversion policies and advance market commitments among others.

That said, there are few generalizable strategies for IP management. Each strategy must be shaped by and respond to the particular parties to each R&D project, the technology involved and the potential research products. A necessary first step in structuring IP management is a case-by-case “due diligence” approach. Such an approach attempts to identify: pieces of IP upon which the success of the project may depend; potential IP bottlenecks or blockages; and, institutions, organizations and/or persons with whom researchers will need to build relationships or with whom they will need to negotiate in order to gain access to that IP. Such a strategy aims to anticipate and avoid IP blockages that could cripple a research project once it is already underway.

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99 See e.g. AIDS Vaccine Clearinghouse, “FAQ: Global Access” online: AIDS Vaccine Clearing House

<[http://www.aidsvaccineclearinghouse.org/access\\_faq.htm](http://www.aidsvaccineclearinghouse.org/access_faq.htm)> which states, “It is hard to imagine a robust AIDS vaccine research enterprise without patent protection, because without patents companies or universities would have little incentive or ability to invest the substantial financial resources required or attract basic funds from others just to proceed.”

100 This may not be the case for other neglected diseases with a predominantly developing country market.

Once products or processes are developed, creative licensing solutions may be used. Humanitarian use licenses are relatively new but likely to become more common especially in the area of neglected disease or vaccine research. For example, licensing strategies can include provisions that provide the licensor or others use the subject matter of the IP for research only; that limit exclusive licenses by geography or by specified use; and that provide for benchmarking of public health goals or development goals. A common IP management strategy is to ensure the licensor or funder maintains a right of reversion (termination of license, march-in rights) to activate upon certain events, such as non-fulfillment of a benchmark or failure to develop a timely or reasonable strategy for developing equitable global access to a product.

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## Glossary

IP management	Intellectual property management
IAVI	International AIDS Vaccine Initiative
AVAC	AIDS Vaccine Advocacy Coalition
IP	Intellectual property
The Gates Foundation	The Bill & Melinda Gates Foundation
MTA	Material Transfer Agreements
Excipient	Any more or less inert substance added to a drug to give suitable consistency or form to the drug; a vehicle
Antigen	Any substance capable of inducing a specific immune response and of reacting with the products of that response
GHAVE	Global HIV/AIDS Vaccine Enterprise
CAVD	Collaboration for AIDS Vaccine Discovery
GAVI	Global Aids Vaccine Alliance
PPPs	Public-Private Partnerships
R&D	Research and Development
PDP	Product Development Partnership
AAVP	African AIDS Vaccine Programme
SAAVI	South African AIDS Vaccine Initiative
EDCTP	European and Developing Countries Clinical Trials Partnership
MVI	Malaria Vaccine Initiative
NVI	Netherlands Vaccine Initiative
CHAVI	Center for AIDS/HIV Vaccine Immunology
DCVMN	Developing Country Vaccine Manufacturers Network
TTO	Technology transfer office
LMI	Low and middle income
CRADA	Cooperative Research and Development Agreements
Reach-through Royalties	Reach-through royalties attempt to capture the value of a discovery before it is a full invention. They are particularly common where the patented product is a research tool that may be useful in developing lucrative inventions.
IPRs	Intellectual property rights
EAL	Equitable Access Licenses
NIH	National Institutes of Health

