

University Contributions to the HPV Vaccine and Implications for Access to Vaccines in Developing Countries: Addressing Materials and Know-How in University Technology Transfer Policy

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ABSTRACT

Human Papillomavirus (HPV) is a major cause of morbidity and mortality worldwide, with most of the disease burden concentrated in developing countries. Over 90 percent of cervical cancer deaths, almost all of which are caused by HPV, occur in low- and middle-income countries where access to goods and services for prevention and treatment pose major barriers to intervention. In resource-poor settings lacking the capacity for routine screening for cervical cancer, the HPV vaccines developed by Merck and GlaxoSmithKline are desperately needed to help prevent these unnecessary deaths. The initial development of currently available HPV vaccines took place at a number of universities and other publicly funded institutions, yet there is little low-cost access to the vaccine in developing countries where access would be most critical. This is the rule rather than the exception with most university-discovered medicines. Universities and other publicly-funded institutions can adopt a number of licensing methods to ensure that vaccines discovered on their campuses are available at low-cost in developing countries. Universities Allied for Essential Medicines has proposed that universities adopt Global Access Licensing policies to implement these changes by enabling generic or low-cost production of the end product in developing countries. Generic competition is a critical market force that has,

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for instance, driven down the price of HIV/AIDS treatments from more than \$10,000 to less than \$99 per patient per year today. While the central barrier to creation of small molecule generics is patent-protection, there are multiple additional barriers that need to be addressed in order to ensure the efficient production of cost-effective generic vaccines and other biologics. While certain biologics may require generic producers to perform additional clinical trials, vaccines are in a somewhat unique situation with respect to both safety and efficacy. With access to appropriate patents, materials and knowledge, vaccines have the potential to be evaluated efficiently and cost-effectively via a pathway parallel to establishing bioequivalence for generic small molecule drugs. A new paradigm is needed that addresses the additional barriers that exist, outside of simply patent protection, to the generic production of vaccines and other biologics. One possible framework, which builds upon previous work on prize funds and patent pools, is discussed here: a Patents, Materials, and Know-how Pool (PMK Pool), based on the patent pool model such as those outlined in the Essential Medical Inventions Licensing Agency and proposals recently put forth by the governments of Barbados and Bolivia. University approaches to licensing vaccines and other biologics need to ensure access not only to patents, knowledge, and materials covered by intellectual property, but must also address the problem of access to materials and know-how that are often proprietary trade secrets. Universities should actively participate in the creation of this and other novel mechanisms, and in the meantime use currently available technology transfer mechanisms to ensure low-cost access to medicines in developing countries.

I. THE HPV VACCINE

A. GLOBAL IMPACT OF CERVICAL CANCER

Cervical cancer causes an estimated 250,000 annual deaths worldwide with an incidence of approximately 500,000 new cases each year.¹ The World Health Organization (WHO) estimates that by 2030 the number of deaths due to this preventable disease will increase to over 400,000.² Persistent infection with Human Papilloma Virus (HPV) is now widely recognized as the major cause of cervical cancer. More than 90 percent of cervical cancer deaths occur in low- and middle-income countries,³ and lack of access to goods and services for cervical cancer screening and treatment pose major barriers to intervention in these areas.⁴ As such, an HPV vaccine has potential to be a particularly effective strategy for addressing cervical cancer in low- and middle-income countries.

¹ Executive Board, World Health Organization, Implementation of Resolutions: Progress Reports, 4 (Jan. 2, 2007) available at http://www.who.int/phi/B120_35_Add1-en.pdf.

² *Id.* at 4.

³ *Id.*

⁴ *Id.*

B. PRODUCTION OF THE HPV VACCINE

Currently available HPV vaccines are designed to mimic the appearance of HPV virus particles. Virus particles are composed of genetic material encased in a protein shell.⁵ These protein shells are frequently constructed from multiple copies of two or three different proteins that assemble into a structure that encases the viral genome.⁶ In the case of HPV, a protein called L1 is the major component of the protein shell.⁷ The L1 protein makes up the outermost layer of the HPV virus – the part of the virus that is first exposed to the body upon infection – and is therefore a primary target for the immune system.⁸ Immune responses directed at the L1 protein are able to confer protective immunity to HPV infection.⁹

The two HPV vaccines currently on the market are both composed of HPV “virus-like particles” (VLPs).¹⁰ HPV VLPs consist of only the L1 protein shell.¹¹ The VLPs are empty, lacking the HPV genetic material that would usually be contained inside.¹² These VLPs, sometimes referred to as “ghost” particles, look like the HPV virus from the outside, but are unable to replicate in the body because they lack genetic material. They are thus unable to establish an infection or induce infected cells to become cancerous, and present minimal safety concerns.

It is important to note that HPV VLPs fall into the category of biologics rather than small molecule drugs, and the implications of this distinction are central to a discussion of HPV vaccine production. The two most important differences between small molecules and biologics relate to production process and size. The majority of currently available medicines are small molecule drugs. These drugs are organic compounds that can be synthesized through a series of chemical reactions. The particular set of chemical reactions used to synthesize a small molecule drug does not affect the properties of the end product, and there are usually a number of different pathways that can produce identical end products. Biologics, on the other hand, are produced using living cells. Unlike with small molecule drugs, the structure of the end product is highly dependent on the production process, and different production pathways cannot necessarily be expected to yield identical end products. There are a number of different types of biologics (e.g.: therapeutic proteins, vaccines), and while they vary greatly in size, they are generally several orders of magnitude larger than small molecule drugs. For example aspirin, one of the most widely used small molecule drugs, is approximately 200 times smaller than Epogen, a commonly used biologic. The HPV L1 protein is around 300 times the size of aspirin, and an HPV VLP particle composed of multiple copies of the L1 protein is over 100,000 times the size of aspirin. The ramifications of these differences in the context of

⁵ FIELDS VIROLOGY 59 (David M. Knipe et al. eds., 5th ed. 2007).

⁶ *Id.* at 513.

⁷ *Id.* at 2302.

⁸ *Id.*

⁹ *Id.* at 513.

¹⁰ *Id.* at 2339.

¹¹ *Id.*

¹² *Id.*

improving access to HPV vaccines will be discussed in further detail in Section III.

C. HPV VACCINES AND UNIVERSITY RESEARCH

Research done at universities was critical in providing the basis for the creation of HPV vaccines. In 1991, a group from the University of Queensland first demonstrated that HPV L1 and L2 proteins could self-assemble into VLPs.¹³ In 1992, a group from Georgetown University showed that the HPV VLPs made up of L1 retained the structural properties of normal HPV virus particles critical for the successful induction of immune responses, indicating that the L1 protein might be a feasible vaccine target.¹⁴ Also in 1992, a group from National Cancer Institute conducted a critical proof of concept study with bovine papillomavirus showing that L1 could assemble into correctly shaped VLPs, and that these VLPs induced high levels of neutralizing antibodies.¹⁵ The following year, this group showed for the first time that HPV L1 by itself could self-assemble into VLPs that induced neutralizing antibodies.¹⁶ Currently marketed HPV VLP vaccines are produced by expressing high levels of the L1 protein inside cells.¹⁷ Multiple copies of the L1 protein then spontaneously self-assemble into the HPV VLPs that resemble the HPV viral protein shell, which can then be extracted from cells, purified, and formulated as an injectable vaccine.¹⁸ The core concept of the HPV vaccine – expressing the L1 protein in cells and allowing it to self-assemble into VLPs – remains virtually unchanged through the transition from university to industry.

D. CURRENTLY AVAILABLE HPV VACCINES

Georgetown University, the National Cancer Institute, the University of Queensland, and the University of Rochester all did parallel research throughout the 1990s on the HPV L1 protein that led to the initial vaccines marketed by Merck and GlaxoSmithKline (GSK).¹⁹ Merck and GSK cross-licensed the patents of all of the involved institutions,²⁰ and, in 2006, Merck's Gardasil was the first vaccine against HPV to reach the market.

¹³ Jian Zhou et al., *Expression of Vaccinia Recombinant HPV 16 L1 and L2 ORF Proteins in Epithelial Cells is Sufficient for Assembly of HPV Virion-like Particles*, 185 *VIROLOGY* 251, 251 (1991).

¹⁴ Shin-Je Ghim et al., *HPV-1 L1 Protein Expressed in cos Cells Displays Conformational Epitopes Found on Intact Virions*, 190 *VIROLOGY* 548, 548 (1992).

¹⁵ R. Kirnbauer et al., *Papillomavirus L1 Major Capsid Protein Self-Assembles into Virus-Like Particles that are Highly Immunogenic*, 89 *PROC. NAT'L ACAD. SCI. USA* 12180, 12180-4 (1992).

¹⁶ R. Kirnbauer et al., *Efficient self-assembly of human papillomavirus type 16 L1 and L1-L2 into virus-like particles*, 67 *J. VIROL.* 6929-36 (1993).

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ Caroline McNeil, News, *Who Invented the VLP Cervical Cancer Vaccines?*, 98 *J. NAT'L CANCER INST.* 433, 433 (2006).

²⁰ *Id.*

21 Gardasil is designed to protect against HPV strains 16 and 18, which are believed to cause 70 percent of worldwide cervical cancer disease burden, as well as strains 6 and 11, which cause 90 percent of genital warts cases.²² As of December 2007, Gardasil sales had reached \$1.5 billion, with 4Q 2007 sales of \$339 million and more than 20 million doses of vaccine distributed worldwide since its market launch in June 2006.²³ Gardasil has generated \$401 million of sales in 3Q 2008²⁴ and has been approved in 106 countries, many under fast track or expedited review.²⁵

Merck's entry price for its quadrivalent vaccine in industrialized countries is high relative to other vaccines. Merck has priced its vaccine at approximately \$125 per dose, or around \$375 for the three-dose series, for the United States market, and at similar levels in other industrialized countries.²⁶ The reduced price for the Centers for Disease Control and Prevention (CDC) Vaccines for Children Program is over \$100 per dose, making Gardasil the most expensive vaccine on the CDC's list for the Vaccines for Children Program.²⁷ Despite the disproportionate burden of cervical cancer in developing countries, the price of Gardasil puts it well out of reach of most poor nations. According to one analysis, "Without a doubt, one of the greatest barriers to the introduction of this vaccine is price . . . dramatic price tiering will be required to facilitate its timely use in developing countries."²⁸

II. THE ROLE OF UNIVERSITIES

A. IMPORTANCE OF UNIVERSITIES TO MEDICINE AND VACCINE DEVELOPMENT

Universities played a critical role in the development of the HPV vaccine. Universities have been, and continue to be the incubators of the biotechnology industry. Much of the initial recombinant DNA technology that has been critical to the biotechnology revolution was developed at Stanford and the University of California, San Francisco. Universities have been key participants in the development of novel biologics such as cancer treatments, hormones and vaccines. According to one study, counting small molecule and

²¹ Press Release, Merck, FDA Approves Merck's GARDASIL® to Protect Against Two Additional Cancers (Sept. 12, 2008) *available at* http://www.merck.com/newsroom/press_releases/product/2008_0925.html.

²² Janelle L. Grimes, *HPV Vaccine Development: A Case Study of Prevention and Politics*, 34 *BIOCHEMISTRY & MOLECULAR BIOLOGY* ED. 148, 151 (2006).

²³ Event Brief, Merck, 4Q 2007 Merck & Co., Inc. Earnings Conference Call - Final (2007), *available at* http://insurancenewsnet.com/article.asp?n=1&neID=20080130560.2_16e40cd824e653c3.

²⁴ Transcript, Merck & Co. Inc. Q3 2008 Earnings Conference Call (Oct. 22, 2008) *available at* <http://seekingalpha.com/article/101228-merck-co-inc-q3-2008-earnings-conference-call-transcript?page=1>.

²⁵ Press Release, Merck, *supra* note 21.

²⁶ Centers for Disease Control and Prevention, *HPV Vaccine Information for Young Women*, <http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-young-women.htm> (last visited April 2, 2009).

²⁷ Centers for Disease Control and Prevention, *CDC Vaccine Price List*, <http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm#pediatric> (last visited Nov. 2008).

²⁸ Jan M. Agosti & Sue J. Goldie, *Introducing HPV Vaccine in Developing Countries - Key Challenges and Issues*, 356 *NEW ENG. J. MED.* 1908, 1909 (2007).

biologic medicines as well as in vivo diagnostics since 1980, 131 different medical innovations have originated in academic institutions.²⁹ For instance, doxil and erbitux, both cancer treatments, humatrope, a synthetic form of human growth hormone, as well as recombivax, a hepatitis B vaccine, were all discovered at the University of California.³⁰ The University of Rochester and the University of Washington contributed to the discovery of recombivax while imatinib mesylate, marketed as Gleevec, a treatment for cancer, originated at the Oregon Health and Science University.³¹ In 2006 alone, universities launched over 550 new start-ups, the majority involving biotechnology.³²

A recent study analyzing biotech patenting³³ found that the top three patenting organizations were the Japan Science and Technology Agency, the University of California, and the United States government (mainly the National Institutes of Health) – all publicly funded institutions. The highest ranking company, Genentech, which was originally founded by scientists from UCSF, is fourth and Millennium Pharmaceuticals is ranked sixth. But overall, American universities dominate the list of the top twenty biotech patenting organizations. The role of universities in the development of biologic drugs is arguably much more central than their role, historically, in the development of small molecule drugs. While the contribution of universities to small molecule drugs is frequently the identification of a potential drug target rather than the creation of an early stage drugs itself, with biotechnology universities are equipped to create the early stages of the eventual medicine that will be refined, but not necessarily fundamentally changed by the licensee, as is the case with the HPV vaccine.

Given their critical importance in the development of biotechnology, there is great potential for universities to have a major impact on access to these vaccines and other biologics. Universities that conduct biomedical research, as non-profit entities dedicated to the creation and dissemination of knowledge for the public good, are ideally suited to address the dire needs of the estimated 10 million people who die each year because they do not have access to existing medicines and vaccines.³⁴ Many universities have recognized the impact they can have on improving access to medicines that originate on their campuses. In March 2007, a group of universities issued an aspirational statement known as the “Points to Consider,” which set out principles to consider as universities patent and license medicines.³⁵ Discussing the need

²⁹ April E. Effort & Ashley J. Stevens, *Using Academic License Agreements to Promote Global Social Responsibility*, 43 LES NOUVELLES: J. LICENSING EXECUTIVES SOC'Y 85, 87 (2008).

³⁰ Jonathan J. Jensen et al., *The Role of Public Sector Research in the Discovery of New Drugs*, Poster at Annual Meeting, Association of University Technology Managers, San Francisco, CA, March 2007.

³¹ *Id.*

³² ASS'N UNIV. TECH. MANAGERS, LICENSING SURVEY FY2006 4 (2006).

³³ GARETH WILLIAMS, JAMES ROBERTSON, & MIKE GILBERT, MARKS & CLERK BIOTECHNOLOGY REPORT 2007 (2007).

³⁴ WORLD HEALTH ORG., *Equitable Access to Essential Medicines: A Framework for Collective Action*, in POLICY PERSPECTIVES ON MEDICINE 1 (2004).

³⁵ White Paper, Cal. Inst. Tech. et al., *In the Public Interest: Nine Points to Consider in Licensing University Technology*, 1 (2007), available at <http://otl.stanford.edu/industry/resources/whitepaper-10.pdf>.

for improved access to medicines in developing countries, the paper explains, “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.”³⁶ To date, 63 universities and associations have endorsed the principles.³⁷ However, few have taken concrete action to leverage their technology transfer activities in order to systematically improve access to medicines and vaccines in developing countries. The consequences of this inaction are highlighted by the current inaccessibility of the HPV vaccine – which universities were so instrumental in developing – to populations of poor countries.

B. WHAT WENT WRONG WITH THE HPV VACCINE?

In the case of the HPV vaccine, each public research entity involved in the initial research of the vaccine granted worldwide exclusive licenses to the technologies that each contributed to commercial entities.³⁸ Given that all of the commercial partners involved were based in rich countries and obtained exclusive licenses, little incentive existed for development of the vaccine for low-cost sale in low- and middle-income countries. The universities missed a critical opportunity in transferring technology to implement strategies that could have improved low-cost provision of the HPV vaccine in developing countries, where it would be the most beneficial. Unfortunately, despite the tremendous benefit the HPV vaccine could have in developing countries, at over \$350 for the three required injections,³⁹ it is too expensive to be widely available. Estimates indicate that each dose may need to cost as little as \$1 to \$2 to make the vaccine cost-effective and affordable in countries with a per capita gross domestic product of less than \$1,000.⁴⁰

A new generation of HPV vaccines, more suitable for the developing country contexts, is currently under development. Some of these new vaccines are intended to be both prophylactic and therapeutic, while eliminating cold chain issues allowing for wider disbursement in developing countries.⁴¹ Once again, public institutions are taking the lead in developing these critical new vaccines. These include Georgetown University, University of Colorado, the Ludwig Cancer Center in Brazil, and the German National Cancer Center, this time supported by the Gates Foundation.⁴²

Though the humanitarian mandate of the Gates Foundation will presumably require the new vaccine to be made available at low-cost in developing countries, universities have the ability to systematically correct

³⁶ *Id.* at 8.

³⁷ Ass'n Univ. Tech. Managers, Endorse the Nine Points to Consider, http://www.autm.net/source/NinePoints/ninepoints_endorsement.cfm (Apr. 3, 2008).

³⁸ Andreas Billich, *HPV vaccine MedImmune/GlaxoSmithKline*, 4 CURRENT OPINION IN INVESTIGATIONAL DRUGS 210-13 (2003); Grimes, *supra* note 22, at 2 (noting that Commonwealth Serum Laboratories, a commercial partner of the University of Queensland, retained the rights in Australia and New Zealand).

³⁹ Amy Gardner, *Drugmaker Assists in Pushing for Mandate for HPV Vaccination*, WASH. POST, Feb. 11, 2007, at C05.

⁴⁰ Agosti & Goldie, *supra* note 28, at 1909.

⁴¹ Stacie Bloom, News, *Q & A with the man who can stop cervical cancer in its tracks*, 115 J. CLINICAL INVESTIGATION 2587, 2587 (2005).

⁴² *Id.*

access inequalities pervasive in developing countries for technologies discovered at universities. As originators of key research and intellectual property that leads to the creation of vaccines and other biologics, universities are well placed to reduce barriers to access. The HPV vaccine, given the tremendous amount of input from the public sector, stands as a stark example of why universities should intervene.

C. WHAT UNIVERSITIES CAN DO

Current attempts to reduce barriers to access for vaccines in resource poor settings, though laudable, have not adequately sought to address systemic problems with the current R&D system that creates high prices in the first place. Indeed, where universities are concerned, the message on access has been mixed. The American Association of Universities, for example, has sought to create further barriers to access by encouraging 12 years of data exclusivity for follow-on biologics as part of legislation under consideration in Congress.⁴³ This is in contrast to the five years of data exclusivity in place for small molecule drugs, and despite the facts that the mean development time for biologics is only 7.4 months longer, and the break-even lifetimes are virtually identical.⁴⁴ This stance, which would bolster companies' bottom lines, threatens to unduly delay the onset of cheaper follow-on biologics after patent expiration.

While useful post-hoc solutions such as the Generic Open License have been proposed for systematic low-cost provision of the current HPV vaccine and other cases in which technology licensing has already occurred,⁴⁵ universities, as noted themselves in the "Points to Consider," can effectively address developing country access by coming to agreement on how to ensure access before legally tying their hands by formalizing licenses with commercial partners.

Universities Allied for Essential Medicines (UAEM), a student-led organization that seeks to make university medicines available at low cost in developing countries, has sought changes in university licensing policy. UAEM has proposed that universities adopt Global Access Licensing policies which would provide a flexible means by which universities would systematically ensure inclusion of licensing terms to promote low-cost access to university discovered medicines in low- and middle-income countries based on the specific technology and particular commercialization needs.

Though there are a number of acceptable legal mechanisms to achieve low-cost provision of medicines, a Global Access Licensing policy should be based on several principles:

(1) The policy should acknowledge that the primary goal of technology transfer is access to the fruits of university research rather than simply

⁴³ Letter from Robert Berdahl, President, American Association of Universities, to US Representatives Anna Eshoo and Joe Barton (June 10, 2008), www.aau.edu/WorkArea/showcontent.aspx?id=6130.

⁴⁴ Henry Grabowski, *Outlook: Follow-on biologics: data exclusivity and the balance between innovation and competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 479-88 (2008).

⁴⁵ Kevin Outterson & Aaron S. Kesselheim, *Market-Based Licensing for HPV Vaccines in Developing Countries*, 27 HEALTH AFFAIRS 130, 130-39 (2008).

revenue creation. Creating this balance better reflects the non-profit mission of the university than does the traditional measure of revenue generation.

(2) The legal methods employed should ensure low-cost access to the final end product.

(3) The policy should recognize generic production as the primary path for low-cost provision. Generic competition has been a central force in reducing the cost of medicines. For instance, U.S. Food and Drug Administration data shows that,

[o]n average, the first generic competitor prices its product only slightly lower than the brand-name manufacturer. However, the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price. As additional generic manufacturers market the product, the prices continue to fall, but more slowly. For products that attract a large number of generic manufacturers, the average generic price falls to 20 percent of the branded price and lower.⁴⁶

In the case of HIV/AIDS medicines, generic production has caused price reductions from \$10,000 in 2000 to about \$99 today.⁴⁷ Given the tremendous barriers to access that price creates, generic production can be a powerful force in creating better health outcomes for those in developing countries.

(4) The policy should address follow-on patents and data exclusivity that arise as part of commercialization of a medicine once a technology has been licensed from the university. Using various legal mechanisms including the grant-back of rights to follow-on patents included in the final medicine or vaccine held by the manufacturer of a medicine, the university can ensure access for a generic manufacturer to the final set of patents needed to generically produce a medicine.⁴⁸

In its implementation, the Global Access Licensing policy should be systematic in order to ensure access to all health-related technologies and include both medicines for communicable and non-communicable diseases. While efforts to improve access to medicines for communicable diseases such as HIV/AIDS are typically emphasized, often forgotten are the numerous deaths caused by non-communicable diseases. For instance, from 2004 to 2030 the World Health Organization (WHO) predicts that heart diseases and stroke will remain the top two causes of death in the world. During the same period, the WHO predicts that a strong increase in deaths from non-

⁴⁶ U.S. Food and Drug Administration, *Generic Competition and Drug Prices*, (2006), available at http://www.fda.gov/cder/ogd/generic_competition.htm, (last visited Nov. 18, 2008).

⁴⁷ Medecins Sans Frontieres, *Untangling the Web of Price Reductions: A Pricing Guide for Developing Countries*, available at <http://doctorswithoutborders.org/publications/reports/2005/untanglingthewebv8.pdf>.

⁴⁸ See, for example, Effort and Stevens for a discussion of licensing mechanisms that can achieve this end. One example provided by Effort and Stevens achieves this by altering the standard definition of “patent rights” in the licensing terms to include follow-on patents for the purposes of executing the universities access policy. Effort & Stevens, *supra* note 29, at 85-101. For a discussion of capturing future improvements through a grant-back mechanism see, Amy Kapczynski et al, *Addressing Global Health Inequities: An Open-Licensing Approach for University Innovations*, 20 BERKELEY TECH. L.J. 1031 (2005).

communicable diseases will be juxtaposed with a strong decline from deaths caused by communicable diseases.⁴⁹

Finally, the program should be sufficiently transparent to verify its effectiveness and use metrics that measure success by the program's impact on access to medicines and the enabling of innovative research. Sorensen and Chambers have argued that using access metrics to measure the success of a university in ensuring access to knowledge activities better takes into account the nonprofit mission of the university.⁵⁰ Though a number of universities espouse principles that would encourage access, systematic information on the effectiveness or implementation of such principles is sparse.⁵¹

III. GENERIC PRODUCTION AND THE BROADER IMPLICATIONS FOR FOLLOW-ON BIOLOGICS: POST- PATENT MONOPOLIES

A. CELL EXPRESSION SYSTEMS AND "REVERSE ENGINEERING" VACCINES

Given the critical importance of generic production to cost-reduction, it is important to discuss the possibilities regarding production of "generic" HPV vaccines as there are a number of unique variables that university policies need to be cognizant of when addressing this issue. While there is a clear paradigm for the production of small molecule generics, there are a number of important issues related to ensuring the efficient and cost-effective production of generic vaccines and other biologics that are not addressed within this framework. Because of some of these differences, as will be discussed below, it is currently not possible to produce "true" generic biologics, and so generic biologics are generally referred to as follow-on biologics.

In the case of vaccines and other biologics, provision of follow-on biologics is relatively new and not nearly as well understood as generic production of small molecule drugs, and universities will thus need to take into consideration a wider range of variables that may influence access. Patents are the central barrier to production of small molecule generics, and as such, patent protection was a primary focus of the Hatch-Waxman Drug Price Competition and Patent Term Restoration Act.⁵² Once patent protection has been lifted, generic producers of small molecule drugs generally do not need any additional information or materials in order to produce an exact

⁴⁹ World Health Organization, *World Health Statistics 2008*, available at http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf.

⁵⁰ Jill Ann Tarzian Sorensen & Donald A. Chambers, *Evaluating Academic Technology Transfer Performance by How Well Access to Knowledge is Facilitated-Defining an Access Metric*, 33 J. TECH. TRANSFER 534, 541-43 (2007).

⁵¹ The annual survey by the Association of University Technology Managers (AUTM) (one of the largest systematic surveys of university technology transfer activity), for instance, only measures metrics such as the number of patents, licenses executed and revenues received from licensing activity. The Association of University Technology Managers, <http://www.autm.net/surveys/> (last visited Mar. 30, 2009). The Better World Project, also led by AUTM, offers vignettes on university technology transfer activities that have helped society but there is no related, systematically collected data. The Better World Project, <http://www.betterworldproject.net/reports.cfm> (last visited Mar. 30, 2009).

⁵² Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No.98-417, 98 Stat. 1585 (1984).

replica of the originator product. With regard to vaccines and other biologics, there are multiple additional barriers – many of which are often not patented – that need to be addressed in order to ensure the efficient creation of cost-effective generics. According to one analysis, “the master cell lines and details of manufacturing processes involved in producing an originator product are fiercely guarded corporate secrets and are not part of the patent, but are the property of the originator company. In fact, not patenting the process makes it unavailable for straightforward replication.”⁵³

Unlike small molecules, where the techniques to demonstrate that a generic is identical to an originator product are well-established and relatively simple, it is difficult to demonstrate that two biologic products are exactly identical. Biologics are orders of magnitude larger and far more complex than small molecule drugs, and it is currently not possible to characterize their structure with the same degree of precision. Determining protein structure is a complex and time consuming process; entire Ph.D. theses are written on structure determination of a single protein. Furthermore, accurately characterizing molecules attached to the surface of the protein, such as carbohydrates, can be extremely difficult.

Even if it were possible to determine protein structure with a high degree of precision, one would not necessarily expect the structure of a biologic manufactured by generic producers to be exactly identical to the originator product, which is why they are referred to as “follow-on” biologics rather than generics. The major difference between generic production of small molecule drugs and biologics is the importance of the production process to the end product. With small molecule drugs, the exact process by which the molecule is produced does not affect the structure of the end product. Generic and brand name small molecule drugs may be produced by very different series of chemical reactions, but still be expected to be structurally identical. With biologics, however, the structure of the end product is highly dependent on the production process. The production process can affect several variables that are important determinants of protein immunogenicity – how the immune system responds to the protein – which is a very important factor with regard to both safety and efficacy of follow-on biologics. Firstly, the production process can significantly affect the three-dimensional conformation of a protein, which is critical to its immunogenicity because it determines which parts of the protein are on the protein surface and thus exposed to the immune system. Furthermore, the immune system will often respond to a particular three-dimensional structure, or “conformational epitope,” rather than to a specific linear amino acid sequence. Finally, the production process affects the molecules (e.g.: carbohydrates) that are frequently attached to the protein surface.

Both the folding of a protein into its correct three-dimensional conformation, as well as the presence of attached surface molecules, are highly dependent on the particular cell line that is used to express the protein. For example, the higher immunogenicity of interferon- β expressed in *E. coli* compared with interferon- β expressed in Chinese hamster ovary cells is

⁵³ S. D. Roger & D. Goldsmith, *Biosimilars: it's not as simple as cost alone*, 33 J. CLINICAL PHARMACY & THERAPEUTICS 459, 461 (2008).

thought to be due to the lack of surface carbohydrates attached to the protein when expressed in the *E. coli* system.⁵⁴ In the case of the HPV vaccine, the particular conformation of the L1 protein is important for several reasons. First, the correct three-dimensional conformation of the L1 protein is important for efficient self-assembly of multiple copies of the L1 protein into VLPs.⁵⁵ Second, the immune response to the L1 protein is directed at particular L1 conformational epitopes.⁵⁶ Access to cell lines is central to the production of generic vaccines and other biologics, but is not addressed by the framework for the production of small molecule generics. It is thus important that universities take into account this variable when considering ways to ensure availability of the fruits of their research in developing countries.

B. SAFETY OF FOLLOW-ON BIOLOGICS: VACCINES VS. THERAPEUTIC PROTEINS

There is an ongoing debate regarding the creation of a regulatory pathway for follow-on biologics. A major issue that has been raised is the possible need for additional clinical trial data in order to address safety concerns that are specific to biologics. The central safety concern regarding follow-on biologics is related to their potential immunogenicity – the response a biologic elicits from the immune system; follow-on biologics have much greater potential than generic small molecules to cause the immune system to react in ways that could be harmful to the body. Thus far, the debate about follow-on biologics has focused almost exclusively on therapeutic proteins such as interferons, granulocyte colony-stimulating factor, and erythropoietins. For example, in a recent study published in the *Journal of the American Medical Association* examining safety-related regulatory actions for biologics approved in the United States and the European Union, vaccines were specifically excluded from consideration.⁵⁷ It is important to recognize that there are several different categories of biologics drugs, each with their own specific issues relating to generic production. In particular, the issues surrounding follow-on production of therapeutic proteins are somewhat distinct from those surrounding vaccines.

The major overall concern with follow-on biologics is their potential immunogenicity. In comparison to small molecule generics, follow-on biologics have significantly greater potential to elicit immune responses that could have serious, or even fatal, consequences. Related to this, there are two immunological points of particular relevance to the discussion of safety of follow-on biologics presented below. First, a majority of therapeutic proteins are homologs of important human endogenous proteins. In other words, they are designed to look almost identical to proteins that are normally present in

⁵⁴ M. Karpusas, A. Whitty, L. Runkel, & P. Hochman, *The structure of human interferon-beta: implications for activity*, 54 *CELL AND MOLECULAR LIFE SCI.* 1203, 1203-16 (1998).

⁵⁵ JoAnn A. Suzich et al., *Systemic Immunization with Papillomavirus L1 Protein Completely Prevents the Development of Viral Mucosal Papillomas*, 92 *PROC. NAT'L ACAD. SCI. USA* 11553, 11553-57 (1995).

⁵⁶ Kathryn J. Hofmann et al., *Sequence Determination of Human Papillomavirus Type 6a and Assembly of Virus-like Particles in Saccharomyces Cerevisiae*, 209 *VIROLOGY* 506, 506-18 (1995).

⁵⁷ Thijs J. Giezen et al., *Safety-related Regulatory Actions for Biologicals Approved in the United States and the European Union*, 300 *JAMA* 1887, 1887-96 (2008).

the body. For example, Type I diabetics fail to produce insulin, so recombinant insulin is produced and administered to the patient to replace insulin that they are unable to produce themselves. Second, the immune system was designed to recognize and destroy “non-self” entities introduced into the body. This is, for example, why organ transplantation is such a challenge and it is necessary to put people on immunosuppressive drugs to prevent transplant rejection.

As noted above, biologic drugs may be broken down into different categories, two of the most important being therapeutic proteins and vaccines. All biologics have the potential to provoke immune reactions, and this immunogenicity is central to the safety concerns regarding follow-on biologics. This will be discussed first in the context of therapeutic proteins (such as insulin, epogen, interferons, human growth hormone, etc), and then in the context of vaccines. There are three major possible consequences of an immunogenic therapeutic protein biologic.⁵⁸

LOSS OF EFFICACY. The immune system could recognize a biologic drug as “non-self” and develop a reaction against the protein that inactivates it, thereby making the drug ineffective. This is the most common problem with follow-on biologics,⁵⁹ as has been observed in the case of recombinant interferons.⁶⁰ The issue of efficacy as relating specifically to vaccines will be discussed in the next section.

GENERALIZED IMMUNE EFFECTS. This could include allergic reactions, serum sickness, or potentially anaphylaxis. These side-effects are relatively common with biologic drugs historically, but are in sharp decline as a result of stronger regulations regarding product purification, as well as advances in product purification techniques.⁶¹

CROSS-REACTIVITY WITH ENDOGENOUS PROTEINS. This is by far the most serious potential effect of an immunogenic biologic. Therapeutic proteins are often designed to look almost identical to a human endogenous protein with important or essential biologic activity. Immune system targeting of the foreign protein can sometimes result in an immune response that cross-reacts with the endogenous homologous protein because of the close structural similarity. In other words, the immune system can mount a response to the therapeutic protein that also attacks critical proteins in the body. The complexity and potential consequences of this were demonstrated in the case of a number of events of pure red cell aplasia, a severe form of anemia, which was associated with use of a slightly altered formulation of epoietin- α that was introduced to the market in 1998 by Johnson & Johnson. Erythropoietin is an endogenous protein that is necessary for the production of red blood cells.

⁵⁸ Michele Kessler et al., *Immunogenicity of Biopharmaceuticals*, 21 NEPHROL. DIALYSIS TRANSPLANT (Supp. 5) v9, v10-v11 (2006).

⁵⁹ David M. Dudzinski & Aaron S. Kesselheim, *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 JAMA 843, 845 (2008) (citing testimony of Dr. William Hancock, at a hearing before the Senate Committee on the Judiciary, June 23, 2004, available at http://judiciary.senate.gov/hearings/testimony.cfm?id=1239&wit_id=3625 (last visited Nov. 17, 2008)).

⁶⁰ P.A. Patten & H. Schellekens, *The immunogenicity of biopharmaceuticals. Lessons learned and consequences for protein drug development*, 112 DEV. BIOL. 81-97 (2003).

⁶¹ A. Covie & M.K. Kuhlmann, *Biosimiliars: Recent Developments*, 39 INT. UROL. NEPHROL. 261, 262 (2007).

This altered formulation of epoietin- α induced the production of an antibody that cross-reacted with endogenous erythropoietin, causing a severe aplastic anemia to ensue.⁶² A similar situation has been reported in the case of megakaryocyte-derived growth factor (MDGF), when antibodies against the recombinant protein also neutralized endogenous thrombopoietin, leading to severe platelet deficiency.⁶³

Issues relating to the safety of follow-on vaccines are somewhat distinct from those described above for therapeutic proteins. The human immune system was designed to identify and destroy pathogenic microbes. It was not designed to passively accept the introduction of foreign homologous proteins. There is a reason that we have been successfully vaccinating people for well over a century, but it is only very recently that organ transplantation has been made possible, and remains an extremely complicated process with a very high failure rate. Whereas any immune response is generally undesirable with a therapeutic protein, the entire goal of a vaccine is to induce a strong immune response. When considering potential safety concerns related to follow-on biologics, it is important to consider the issues described above – loss of efficacy, generalized immune effects, and cross-reactivity with endogenous proteins – in the context of the specific case of vaccines.

LOSS OF EFFICACY. If the body develops an immune reaction against a vaccine that inactivates it, it means that a highly desirable goal of vaccination – the induction of a neutralizing antibody response – has been successfully achieved. This is in contrast to a neutralizing antibody elicited against a protein therapeutic that inactivates it such that it can no longer perform its intended function. Still, a follow-on vaccine has a potential loss of efficacy. This could be due to, for example, failure of the protein to fold properly leading to important regions of the protein not being visible to the immune system. This would cause the vaccine ineffective, but does not pose a safety concern.

GENERALIZED IMMUNE EFFECTS. This remains a potential problem for follow-on vaccines, with particular types of vaccines being of potentially greater or lesser concern. In the case of the HPV VLP vaccine, generalized immune effects are likely to be mainly dependent on variables such as the quality of the purification process, the formulation of the end product, or the adjuvant that the vaccine is administered with. Stringent regulations pertaining to the purity of the final product as well as use of identical delivery formulations present ways of addressing this issue.

CROSS-REACTIVITY WITH ENDOGENOUS PROTEINS. Regarding the third issue, the major reason for concern about a protein therapeutic inducing an immune response that will cross-react with endogenous proteins is that the vast majority of protein therapeutics are homologs of human proteins. In other words, they are designed to look extremely similar to important proteins normally present in the body, so it is relatively easy for the immune system to become “confused” and attack the body’s own proteins as well as the

⁶² Sabine Louët, *Lessons from Eprex for Biogeneric Firms*, 21 NATURE BIOTECHNOLOGY 956, 956-57 (2003).

⁶³ T.A. Neumann & M. Foote, *Megakaryocyte Growth and Development Factor (MGDF): An Mpl Ligand and Cytokine That Regulates Thrombopoiesis*, 6 CYTOKINES, CELLULAR & MOLECULAR THERAPY 47, 47-56 (2000).

therapeutic protein. Vaccines, on the other hand, incorporate molecules from microbes that bear little similarity to human proteins. This is, in fact, one of the ways the immune system begins the initial fight against infections: by recognizing and attacking patterns, or antigens, that are highly-specific to microbes. If the immune system were likely to initiate a serious autoimmune attack on the body in response to bacterial or viral antigens, it would be disastrous; major autoimmune reactions could ensue every time someone came down with a cold. In rare cases, it is possible for an infectious microbe to elicit an immune response that coincidentally cross-reacts with the body. Rheumatic fever, for example, is caused by cross-reactivity of the immune response directed at the bacteria streptococcus with tissue in the heart and joints. This type of reaction, however, is extremely rare, and appears to be highly dependent on the particular attributes of the individual host immune system.

C. CORRELATES OF PROTECTIVE IMMUNITY TO HPV: EVALUATING THE EFFICACY OF FOLLOW-ON VACCINES

In order to evaluate the efficacy of a treatment approach, it is necessary to assess the interaction of the treatment effector with the disease target. For small molecule drugs, the effector mechanism is the direct interaction of a chemical compound with a target in the body. This is essentially equivalent to the situation with regard to biologic drugs in the case of therapeutic proteins. In the case of vaccines, however, the effector is not the vaccine itself, but rather the immune system. The formulated vaccine does not interact directly with the disease target, rather it induces the immune system to respond to the disease target rapidly and effectively. As such, the critical determinant of vaccine efficacy is the vaccine-induced immune response. To show that a small molecule generic is equally as efficacious as the originator product, it is necessary to show that the molecular structures of the two drugs are identical in order to confidently predict the same interaction of the treatment effector with the disease target. With regard to vaccines, on the other hand, the relevant parallel in predicting the effector interaction with the disease target would be to show that two vaccines induced an identical immune response.

Demonstration of bioequivalence is a mechanism that allows for efficient, safe, and cost-effective production of generic small molecule drugs without having to repeat clinical trials. Demonstrating bioequivalence for small molecule generics involves showing that the two drugs have identical structures as well as similar bioavailability profiles when administered to humans. For recombinant proteins a similar study would be relevant, however there are difficulties with precise structure determination, and safety concerns about immunogenicity. For vaccines, on the other hand, the parallel study would not evaluate the bioavailability of the vaccine itself, but rather the immune responses induced by the vaccine. Whether two vaccines have precisely identical structures or not, they should be equally effective in conferring protection if they are able to induce identical immune responses. While there are major difficulties involved in an attempt to compare the exact molecular structure of a follow-on vaccine with the originator, making a comparison of vaccine-induced immune responses is much more straightforward.

Two major variables are generally assessed in the evaluation of vaccine efficacy: induced immune responses and protective immunity. Assessment of induced immune responses includes measures of immune response strength, character, and antigen-specificity, but does not involve establishing that administration of the vaccine confers protection from a particular pathogen. The assessment of protective immunity, on the other hand, involves either challenge studies or large human trials to evaluate the ability of a vaccine to protect individuals from a particular infection. Establishing correlates of protective immunity for a particular disease involves developing a clear understanding of the relationship between induced immune responses and protective immunity. Generally, there is a particular response, in terms of both the immune response characteristics (e.g.: antibody versus T-cell) and antigen-specificity, that is responsible for protection. Preclinical studies of HPV L1 VLPs have demonstrated that protection from HPV infection correlates strongly with the presence of neutralizing antibodies directed against the L1 protein.⁶⁴ Further preclinical studies demonstrated that passive transfer of serum containing these antibodies results in protection in unvaccinated controls, providing strong evidence supporting an anti-L1 neutralizing antibody response as protective in HPV infection.⁶⁵ In humans, high titers of anti-L1 neutralizing antibodies are observed after vaccination with HPV VLPs.⁶⁶

Evaluating the ability of a vaccine to induce a specific immune response is far less complex, less costly, and less time-consuming than performing clinical trials to assess the ability of the vaccine to confer protective immunity. An efficacy assessment of generic vaccines that parallels the establishment of bioequivalence for small molecule generics may be envisioned, which could be performed by comparing induced immune responses rather than structure and bioavailability. Once the correlates of protective immunity have been elucidated, the ability of a vaccine to induce this response may be taken as a proxy of its ability to provide protection.

Merck has, in fact, done this in its own HPV vaccine trials. The efficacy of Gardasil was established in trials performed in 16 to 26 year old women. However, due to the infeasibility of efficacy studies in child and early adolescent populations, HPV neutralizing antibody titers were used as a surrogate marker of protection when seeking approval for Gardasil in 9 to 15 year old girls.⁶⁷ It has not yet been shown unequivocally that an anti-L1 neutralizing antibody response confers protection in humans. This is mainly

⁶⁴ Robert S. Lowe et al., *Human Papillomavirus Type 11 (HPV-11) Neutralizing Antibodies in the Serum and Genital Mucosal Secretions of African Green Monkeys Immunized with HPV-11 Virus-like Particles Expressed in Yeast*, 176 J. INFECTIOUS DISEASES 1141, 1144-45 (1997); Kathrin U. Jansen et al., *Vaccination with Yeast-expressed Cottontail Rabbit Papillomavirus (CRPV) Virus-like Particles Protects Rabbits from CRPV-induced Papilloma Formation*, 13 VACCINE 1509, 1509-13 (1995).

⁶⁵ Suzich, *supra* note 55, at 115555.

⁶⁶ Dennis Dias et al., *Optimization and Validation of a Multiplexed Luminex Assay to Quantify Antibodies to Neutralizing Epitopes on Human Papillomaviruses 6, 11, 16, and 18*, 12 CLIN. DIAGN. LAB. IMMUNOL. 959, 959-69 (2005); Luisa L. Villa et al., *Immunologic Responses Following Administration of a Vaccine Targeting Human Papillomavirus Types 6, 11, 16, and 18*, 24 VACCINE 5571, 5580-83 (2006).

⁶⁷ Ian Frazer, *Correlating Immunity with Protection for HPV Infection*, INT. J. INFECT. DIS. S10, S12 (2007).

due to the fact that the gold standard for establishing immune correlates of protection— analyzing vaccine failures — has not been possible because to date all subjects immunized with HPV VLPs have seroconverted and there have thus been very few vaccine failures to analyze.⁶⁸ Despite this lack of absolute proof of the exact nature of correlates of protective immunity, the evidence in support of an anti-L1 neutralizing antibody response is compelling enough that the FDA considered it an acceptable proxy measurement of protective efficacy: “The efficacy of [Gardasil] was studied in four randomized, double-blind, placebo-controlled trials enrolling a total of 20,541 females between the ages of 16 and 26 Anti-HPV antibody responses 1 month Postdose 3 among 9-15 year old girls were non-inferior to anti-HPV responses in 16-26 year old females in the combined database of immunogenicity studies for Gardasil. On the basis of this immunogenicity bridging, the efficacy of Gardasil in 9-15 years old girls was inferred.”⁶⁹

IV. UNIVERSITY BASED SOLUTIONS

The production of follow-on biologics obviously faces issues that are far more complex than the production of small molecule generics. In the specific case of vaccines, due to their somewhat unique situation among biologics with regard to safety concerns and efficacy measures, possibilities may be envisioned for the production of low-cost follow-on vaccines via a pathway that parallels the demonstration of bioequivalence for generic small molecules. The demonstration of bioequivalence has been a very effective mechanism for promoting the rapid and cost-effective production of small molecule generics, and a parallel mechanism for follow-on vaccines could have potential to be similarly effective. Due to the complexities of vaccine production, however, systems that could enable this type of follow-on vaccine production would need to address several additional variables that are not relevant in the case of small molecule generics.

Described below are three early proposals for universities to consider as part of a Global Access Licensing policy for achieving low-cost access in developing countries to vaccines that originate in universities. It should be emphasized at the outset that these three proposals are simply initial suggestions on how several of the complications involved in the production of follow-on vaccines could be addressed, some based on approaches developed for use outside of the university context, and are not meant to be a comprehensive list of possibilities. In addition, the first two proposals present possibilities which could likely be accomplished by universities alone without changes to any national or global framework or creation of new organizations.

Rather than definitively espousing any specific approach, we believe that the important point to acknowledge is that the intellectual property paradigm that has been developed with the production of small molecule generics in

⁶⁸ Margaret Stanley et al., *Prophylactic HPV Vaccines: Underlying Mechanisms*, 24 VACCINE (Supp. 3) S3/106, S3/108 (2006).

⁶⁹ US Food and Drug Administration, Center for Drug Evaluation and Research, Office of Oncology Drug Products, FDA Licenses Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil) for the Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus (2007), <http://www.fda.gov/cder/offices/oodp/whatsnew/gardasil.htm> (last visited Apr. 14, 2009).

mind fails to address several major variables relevant to the efficient and cost-effective production of follow-on vaccines and other biologics. We also acknowledge that universities are present at one point in a chain for production and distribution and do not expect that the approaches we propose here for universities will be able to answer all regulatory, delivery and other systematic difficulties unrelated to universities. We hope that these approaches will present broad frameworks for thinking about how to approach the university role in enabling low-cost production of follow-on vaccines that will spur further exploration. Following a discussion of these three approaches, we compare the relative merits of each as well as the related difficulties that could be encountered in actual implementation.

A. REQUIRE PROVISION OF NEEDED INTELLECTUAL PROPERTY, MATERIALS, AND KNOW-HOW IN LICENSING AGREEMENTS

One of the most direct potential paths for ensuring access to university discovered medicines in developing countries is to obligate industry partners who license the vaccine-related technology from the university to make relevant patents – including those that are subsequently added to university IP – as well as know-how, including production methods, and materials, including relevant cell lines, available to producers who will manufacture the vaccine for use in low- and middle-income countries. In return, the industry licensee could receive royalties from the low-cost producer and maintain monopoly rights in rich countries.

One specific licensing model that would be a useful tool of a Global Access Licensing program that could be used to begin to explore the details of how this proposal might be enacted would be the Equitable Access License (EAL), developed by a working group convened by UAEM.⁷⁰ The grant-back provisions of the EAL capture future improvements or additions to university intellectual property made by industry⁷¹ for use as part of the Global Access program. This is necessary because most medicines include product, process or use patents when they are registered that are beyond university owned IP. The grant-back could be expanded to include unpatented areas of know-how and materials required to produce a vaccine, though the actual transfer could be done through a separate but parallel agreement to the patent licensing agreement. However, as discussed below, enforcement would go well beyond the passive mechanism envisioned in the original proposal.⁷²

In addition to the EAL, another useful licensing model to consider was created by Knowledge Ecology International (KEI) as part of a proposed Essential Medical Inventions Licensing Agency (EMILA). Like the EAL, it would require a grant-back or back-license of patentable improvements made by a generic producer that manufactures the medicine so that other generic

⁷⁰ Universities Allied for Essential Medicines, Model Provisions for an “Equitable Access and Neglected Disease License” Version 1.0, <http://www.essentialmedicine.org/EAL.pdf> (last visited April 2, 2009).

⁷¹ Samantha Chaifetz et al., *Closing the Access Gap for Health Innovations: An Open Licensing Proposal for Universities*, 3 GLOBALIZATION & HEALTH 4 (2007), available at <http://www.globalizationandhealth.com/content/3/1/2>.

⁷² See Kapczynski et al, *supra* note 48, at 1090-91 (describing the self-monitoring system in the EAL proposal).

manufacturers and the original licensor could benefit from the improvement.⁷³

Similar to the grant-back, which captures all the patents included in a medicines discussed above, Efforts and Stevens note that a patent “reach through” mechanism could be employed to enable use of patents developed by the commercial licensee for the purposes of what they call the “Social Responsibility Purpose.” Efforts and Stevens discuss accomplishing this by broadening the definition of patent rights in the license to “include all patents owned or controlled by Licensee that are co-listed with Patent Rights solely or jointly owned by University in the Orange Book”⁷⁴ This means that rights to patents also listed as part of the final formulation of a medicine approved by the U.S. Food and Drug Administration would be accessible to the university for the purpose of implementing its access licensing policy. Similar to the method noted above, this approach of redefining rights in the license itself could be considerably expanded to include data exclusivity, know-how and materials such as cell lines.

Having captured the needed intellectual property, know-how and materials through one of these approaches, the university could then employ an open licensing mechanism similar to those of the EAL or EMILA license which would enable a low-cost producer in any country to access the technology, in the case of the EAL, through a simple notification process, for production of vaccines that could only be distributed in low- and middle-income countries, preserving the current rich-country markets for vaccine sales.⁷⁵ As in the EMILA license, the necessary patents should be available to the low-cost producer on reasonable and non-discriminatory terms in order to encourage generic competition. The EMILA model also deals with regulatory issues by including an additional “Authorization to Reference or Rely upon Health Registration Data” to aid in medicine registration and standards for acceptable manufacturers to ensure the safety of products.⁷⁶ It must be acknowledged, however, that beyond mechanisms for creating low-cost developing country access, which are better understood for small-molecule drugs, new mechanisms would need to be developed for the required sharing of know-how and materials.

Also, these legal mechanisms, expanded in such a way to include areas beyond just patents to areas which are not public information and in fact often trade secrets (such as know-how and materials), would represent a significant expansion and understanding of the scope of traditional licensing activity and would likely meet strong resistance. Also, though a limited number of approaches are specifically mentioned, including the EAL and the redefining of the definitions in the license which expand rights, we acknowledge that any attempt to enact this approach would require flexibility for individual circumstances and the previously outlined methods are discussed as a few of many potential models to revise and build upon.

⁷³ Knowledge Ecology International, The Essential Medical Inventions Licensing Agency, <http://www.keionline.org/misc-docs/emila.pdf> (last visited Apr. 2, 2009) (hereafter “EMILA”).

⁷⁴ Effort & Stevens, *supra* note 29, at 90.

⁷⁵ See Kapczynski et al, *supra* note 48; EMILA, *supra* note 73.

⁷⁶ *Id.*

B. OFFER LICENSES TO UNIVERSITY IP, KNOW-HOW AND MATERIALS TO DEVELOPING COUNTRY MANUFACTURERS

Another approach is for a university to maintain the ability to provide access to patents, know-how and materials that they have created to developing country manufacturers who could enable low-cost access in low- and middle-income countries. This approach would not enable generic-like production of follow-on vaccines, which has historically been a main force in drastic medicine price reductions,⁷⁷ because the generic producer would have to bear the costs of R&D and clinical trials. However, it may offer the opportunity for a manufacturer who must conduct further R&D to produce lower-cost medicines in low- or middle-income countries. Companies operating in the developing country setting may have stronger reasons to develop and market lower-priced medicines because of the consumers where they operate, among other considerations such as operating costs and increased efficiencies. For instance, Shantha Biotechnics based in Hyderabad, India, is using technology developed by Johns Hopkins University and the U.S. National Institutes of Health to produce an HPV vaccine that they expect to market for \$15 per dose despite the R&D that will be required.⁷⁸ In the case of Shantha's earlier hepatitis B vaccine, "Indian patients directly benefited from Shantha's cost-effective and efficient manufacturing process, as Shantha priced their branded Shanvac-B product at \$0.50 per dose, a significant reduction from the \$15 per dose cost of the rival import." Similarly, Biocon of Bangalore, India, priced its recombinant human insulin at approximately half the price of imports prompting international competitors to drastically lower their prices.⁷⁹

This approach could be achieved through a variety of licensing and knowledge sharing arrangements with developing country manufacturers. One study of developing country manufacturers found various arrangements with both multi-national corporations (MNCs) and research and academic institutions. Of the sample of manufacturers examined, "all had academic or research institution partnerships, which accounted for 70 percent of their pipeline products."⁸⁰ In the case of Indian and Brazilian vaccine manufacturers, this reliance on technology transfer from both MNCs and academic and public institutions has been driven by a desire to save costs and

⁷⁷ U.S. Food and Drug Administration - Office of Generic Drugs *Generic Competition and Drug Prices* (2006), http://www.fda.gov/cder/ogd/generic_competition.htm (last visited April 3, 2009); Cf. Medecins Sans Frontieres, *Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries*, at 9, 13-39 (10th ed. 2007), http://www.msf.org/source/access/2007/Untangling_the_Web_10th_ed_2007.pdf (last visited Apr. 4, 2009) (graphing the drop in price for specific drugs after generic drug competition).

⁷⁸ Gunjan Pradhan Sinha, *Shantha Developing \$15 Cervical Cancer Vaccine*, THE ECON. TIMES, Oct. 16, 2007, http://economictimes.indiatimes.com/News/News_By_Industry/Shantha_developing_15_cervical_cancer_vaccine/articleshow/2461640.cms (last visited Apr. 4, 2009).

⁷⁹ Sarah E. Frew et al., *The Role of the Domestic Private Sector in Developing Countries for Addressing Local Health Needs*, 8 INT. J. BIOTECHNOLOGY 91, 100 (2006).

⁸⁰ Julie B. Milstien et al., *Access to Vaccine Technologies in Developing Countries: Brazil and India*, 25 VACCINE 7610, 7615 (2007) (citing Boston Consulting Group, *Global Vaccine Supply: The Changing Role of Suppliers, a Report Commissioned for GAVI by WHO and the World Bank* (2005)).

time, though academic partnerships also allow greater freedom to operate and greater “equity of benefits.”⁸¹

Overall, developing country manufacturers have shown a strong ability to develop and produce vaccines. Data from the study of selected Indian and Brazilian vaccine manufacturers, referenced above, found “A mean of 28 percent (14 - 44 percent, depending on the manufacturer) of new antigens were being developed either by in-house research activities or by technology transfer.”⁸² Shantha Biotechnics’s production capacity is sufficient that it now provides 40 percent of UNICEF’s recombinant hepatitis B vaccine supply.⁸³ As the ability to manufacture vaccines and other biologics in developing countries improves, universities will have ever greater possibilities for creating partnerships and transferring technology directly to emerging market manufacturers.

C. USE OF PATENT POOLS AND PRIZE FUNDS TO INCENTIVIZE AND STREAMLINE KNOWLEDGE SHARING

There is currently a great deal of discussion of the potential for patent pools and prize funds to revolutionize access and innovation for medicines. Patent pools have long been used to share knowledge and aid innovation while providing a streamlined mechanism for collective management of intellectual property and royalty sharing amongst patent holders. Patent pools are used, for example, with the DVD standard which requires many patents from many patent holders, which can then be licensed out as a group to anyone hoping to use standard.⁸⁴ For a number of years, Knowledge Ecology International (KEI, formerly the Consumer Project on Technology), Doctors Without Borders/MSF (MSF), and Essential Inventions have presented proposals and advocated for expanding the use of patent pools to medicines.⁸⁵ Recent success of this advocacy has been seen concretely with the decision by UNITAID to start a patent pool which MSF had originally requested that they create.⁸⁶

Prizes have been discussed in a variety of settings, including in a bill introduced in the United States Senate, as a means by which to create incentives that would inspire production of medicines that improve health outcomes while eliminating monopoly pricing. In the Senate bill, a patent holder, including universities, rather than receiving a monopoly and the

⁸¹ *Id.* at 7615, 7618.

⁸² *Id.* at 7614.

⁸³ Frew et al., *supra* note 80, at 100.

⁸⁴ *See generally* Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools and Standard Setting*, 1 INNOVATION POL’Y & THE ECON. 119 (2001) (discussing patent pools generally).

⁸⁵ *See generally* Knowledge Ecology International, *Patent Pools*, http://www.keionline.org/index.php?option=com_content&task=view&id=63&Itemid=1 (last visited April 4, 2009); Doctors Without Borders / Medecins Sans Frontiers Campaign for Access to Essential Medicines, <http://www.msfaccess.org/> (last visited April 4, 2009); Essential Inventions, Essential Patent Pool for AIDS, <http://www.essentialinventions.org/docs/eppa/> (last visited Apr. 4, 2009).

⁸⁶ Press Release, UNITAID, UNITAID Moves Toward a Patent Pool for Medicines (July 9, 2008), *available at* <http://www.unitaid.eu/en/NEWS/UNITAID-moves-towards-a-patent-pool-for-medicines.html>.

ability to charge monopoly pricing, would receive a potentially substantial prize based on the improved health resulting from a medicine while making the medicines immediately available for generic production.⁸⁷ The corollary effect to giving prizes based on health outcomes of medicines rather than monopoly pricing is that incentives for drug discovery would then be aligned with finding medicines that will improve the health of the most people, rather than narrowly focusing on incremental improvements to medicines which only benefit a narrow group that can afford to pay the highest prices.

While both approaches could be used separately – patent pools to reduce transaction costs and streamline provision of IP to generic producers, and prize funds to motivate research that better reflects global need while ensuring generic production of resulting products – used in conjunction they create an opportunity to simplify production and lower the cost of follow-on biologics.

Though it is in the early stages of development, the governments of Barbados and Bolivia have proposed just this combination. Amongst a number of prize fund proposals made by Barbados and Bolivia is a “Priority Medicines and Vaccines Prize Fund.” Under the terms of the Barbados and Bolivia proposal as currently articulated, the fund would focus on type II and type III diseases, new antibiotics and new threats to public health. While the majority of the funds would be dedicated to “final product prizes” and distributed based on health outcomes resulting from a final medicine, a portion would be dedicated prizes for earlier stages of product development including overcoming roadblocks to research and a separate amount available to researchers who make use of open-source methods including open access publishing and ready sharing of data and technology. Rights from the resulting products would be pooled, and they would include all data and know-how required to produce the medicines.⁸⁸

Under a similar model, universities could license vaccine materials, know-how and patents into a pool, such as the UNITAID pool currently in the planning stages. UNITAID, an international drug purchaser supported by a wide range of governments, will use the pool in its initial stages to bring together the patents of multiple patent owners to allow for the development of low-cost pediatric and fixed dose combinations HIV/AIDS medications. The pool will reduce barriers to generic manufacture of these medicines and each of the patent holders who contribute to the pool will receive royalties.⁸⁹

A pool for vaccine production would need to have a broader scope than simply patents to effectively reduce barriers to production. In order to produce a follow-on vaccine that would gain regulatory approval via a process that truly parallels the demonstration of bioequivalence for small molecules, other patented and proprietary materials and know-how such as cell lines and

⁸⁷ Medical Innovation Prize Fund Act of 2007, S. 2210, 110th Cong. (2007). See also Knowledge Ecology International, *Prizes to Stimulate Innovation*, http://www.keionline.org/index.php?option=com_content&task=view&id=4&Itemid=1 (compiling reports on the use of prize funds and patent pools to spur biomedical innovation while lowering medicine costs through generic production).

⁸⁸ Knowledge Ecology International, *Working Document - Barbados and Bolivia, Proposal 3, Priority Medicines and Vaccines Prize Fund (PMV/pf)*, at 2 (2008), http://www.keionline.org/misc-docs/b_b_igwg/prop3_pmv_pf.pdf.

⁸⁹ Press Release, UNITAID, *supra* note 87.

manufacturing processes would be important. The types of materials and know-how required to produce a vaccine, including any improvements or additions to the original university IP, could be centrally provided from the pool, allowing multiple manufacturers to have access to all of the information and materials necessary to manufacture the vaccine. In this patent, materials and know-how (PMK) pool, similar to the mechanism proposed in the Barbados and Bolivia proposal or the EMILA mentioned above, a central entity could act as a repository for all the information necessary to manufacture low-cost vaccines. The pool would also need to consider what mechanisms must be adapted to share any materials and know-how that might be required.

In order to induce universities and industry to participate in this approach, strong incentives would be necessary. The most commonly used mechanism for repaying a patent holder is the ability to earn further royalties from medicines, though developing countries currently represent an extremely small portion of the entire pharmaceutical market. At present, the entire market of low- and middle-income countries consists of only five to seven percent of pharmaceutical revenues⁹⁰ while at universities, “the ratio of net licensing income to sponsored research levels is usually small, approximately 5 percent or less.”⁹¹ This means that a relatively miniscule portion of university revenue of top schools derives from developing countries. Given that this is standard repayment for a university, further incentive beyond royalties may be unnecessary.

However, in the context of a patent pool, in addition to focusing research on medicines which will improve health due to the way a prize as discussed above is rewarded, a prize fund could potentially offer a needed incentive beyond royalties to induce the developer of a medicine to participate in the pool. This is particularly true given additional elements of what the developer would be providing to the pool (know-how and materials) beyond patents and is recognized in the Barbados and Bolivia proposal.

Universities, among other potential modes of engagement, could license their discoveries into such a pool and require that any future improvements in IP, materials or processes be put back into the pool. With the hope of receiving a prize, industry could also be further motivated to participate and provide the full range of materials necessary for follow-on generic-like production of a vaccine. Industry, in regard to the UNITAID patent pool specifically, has expressed interest in participating, one noting a number of potential benefits to their operations and raising the possibility of a prize fund being used in conjunction with the pool.⁹²

⁹⁰ Chaifetz et al., *supra* note 71, at 2 (citing Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2005 – From Laboratory to Patient: Pathways to Biopharmaceutical Innovation* (2005)).

⁹¹ Gregory K. Sobolski et al., *Technology Licensing: Lessons from the US Experience*, 294 JAMA 3137, 3138 (2005).

⁹² James Love, *UNITAID Patent Pool at Mexico City AIDS Conference*, KEI POLICY BLOG, August 6, 2008, http://www.keionline.org/index.php?option=com_jdwp&Itemid=39&p=135 (last visited Apr. 4, 2009).

D. COMPARISON OF APPROACHES

In considering the approaches discussed above, we must first recognize that universities occupy an important place in drug discovery, but also must consider what they can implement alone and what requires larger structural changes or the creation of new institutions. Universities possess limited technology transfer resources, and would likely find difficulty in handling day-to-day operations of a PMK pool. Also, we must consider what motivates a university and mechanisms it can participate in, taking into account the timeframe in which each of these solutions can be enacted.

A licensing approach that ensures access to all of the final intellectual property, materials and know-how required to produce a vaccine is desirable in a number of ways. This approach could work largely within the current intellectual property system and is technically feasible. However, though theoretically not insurmountable through the collective action of universities, this approach would likely be strongly resisted given the dramatic expansion of information, knowledge and materials beyond IP that would be required to be shared.⁹³

Technical issues surrounding the sharing of know-how and materials would also need to be addressed. Would visits from low-cost manufacturers be arranged, or could information be stored in a central repository? Also to be addressed would be the sharing of materials, including cell lines. Either the university or the licensee would need to create a mechanism for materials transfer. Much of the key know-how in terms of methodology and vaccine formulation may end up being highly specific to the particular vaccine under production. Sharing of cell lines optimized for the production of a specific vaccine, however, could pose major issues of confidentiality for other company products if the master cell line is used to produce a number of different vaccines or biologic drugs.

Beyond the technical issues, enforcement of such an agreement would be extremely difficult. As previously noted, the passive enforcement of the EAL would potentially need to be more active given that patents are by design public information, while know-how including manufacturing processes and cell lines are often trade secrets. If a licensee did not provide adequate information or make materials available, the university might have to actively seek to enforce the terms of the agreement, which could be problematic in many ways.

Given the challenges involved in requiring a licensee to provide all that is needed to produce a follow-on vaccine to a generic manufacturer, a good deal of further exploration is necessary to evaluate how to overcome these challenges. However, these challenges could likely be met without the creation of new institutions and largely within the framework in which universities currently operate. This provides the added advantage that such an approach could theoretically be implemented in the near term.

As developing country manufacturers become increasingly able to develop and manufacture vaccines, the possibility of providing access to university discoveries for development and production in low- and middle-income

⁹³ See Kapczynski et al., *supra* note 48 (discussing the difficulties of expanding access requirements beyond patents).

countries would seem like a crucial new pathway. However, an important drawback with this approach is that it does not maximize the impact of the work done by entities that have already invested considerable effort to optimize large-scale manufacturing methods and take the vaccine through clinical trials, much of which would have to be repeated by the new manufacturer. This means that most of the cost savings associated with traditional generic production would be lost. Also, because this method would not encourage competition among multiple manufacturers, the same downward price pressures would not exist. Though the proposed Shantha vaccine at \$15 would be a drastic reduction in price compared to the current vaccines, in order to be widely available in developing countries, a lower price would likely still be needed.⁹⁴ It is therefore less desirable in its outcome to the previous proposal.

Nonetheless, as with the approach outlined above, universities could, and to some extent already do undertake deals with developing country manufacturers. This means little change in operations or cost for the university, and such an approach could be implemented in the near term.

The use of PMK pools and prize funds answers both of the downsides of each of the previous approaches. Both the proposal to compel licensees to make all needed patents, materials and know-how available and the PMK pool proposal attempt to facilitate efficient and cost-effective production of follow-on vaccines. They accomplish this in the sense that the manufacturer could build upon the initial work done by the original manufacturer, enabling them to use a pathway parallel to that of establishing bioequivalence for small molecule generics to seek regulatory approval. This avoids the expense of large clinical trials to establish that the vaccine confers protective immunity.

While creating a forum for knowledge sharing that would enable access to the knowledge required to manufacture a follow-on vaccines in this manner, the prize should attempt to offer the incentives required to bring manufacturer improvements into the pool. Though technical questions still remain, such as how know-how and materials would be shared, this systematic approach should be evaluated by universities as they consider a way forward for Global Access Licensing for vaccines.

This approach seeks not only to improve generic production, but also to realign the R&D agenda to reflect the health needs of the global population rather than the current narrow R&D priorities. Universities should proactively participate in developing and participating in the UNITAID and Barbados and Bolivia proposals, and the discussion surrounding the operational aspects of a PMK pool generally. Universities and their researchers stand to benefit from the prizes and ease in achieving their non-profit mission by streamlining their ability to make their medicines available at low-cost in developing countries. By participating in such a program, universities would enable cost-effective manufacture of follow-on vaccines, enabling follow-on competition to create lower prices.

Acknowledging the downsides of such a proposal with regards to what a university is able to accomplish on its own, universities must interact collaboratively with other organizations to see this proposal come to fruition

⁹⁴ Agosti & Goldie, *supra* note 28, at 1908-10.

given the tremendous potential pay-offs. This approach may take time to get off the ground and therefore the licensing proposals previously presented might represent important stop-gap measures in the near-term.

Recognizing the limitations of this paper, a number of pull mechanisms were not discussed while exploring these options, particularly in the first two proposals. Prize funds could be paired with any of the proposals as could work in collaboration with countries to issue compulsory licenses. However, given our desire to focus primarily on ways universities specifically can engage, we have purposefully limited our exploration and tried to find proposals which could be implemented in the short term by the universities along with a longer term vision of better options.

Beyond the UNITAID pool and Barbados and Bolivia proposals, the WHO recently adopted World Health Assembly Resolution 61.21, a global strategy for improving both access to and innovation for medicines. The resolution includes recommendations to explore and develop a variety of methods to improve access and innovation including open-licensing, patent pools and prize funds.⁹⁵ On a concrete level, the X PRIZE Foundation, with the support of the Bill and Melinda Gates Foundation, is currently exploring the development of a prize fund for a low-cost tuberculosis diagnostic appropriate for the developing country setting.⁹⁶

In addition to actively participating in the development of current knowledge pooling efforts, universities should start exploring and adopting various strategies in the short-term that improve access to vaccines in developing countries. Learning from the lessons of the HPV vaccine, universities must realize the important steps they can take now – in recognition of their mission to create and disseminate knowledge for the public good – to ensure low-cost access to vaccines developed on their campuses.

CONCLUSION

Current R&D, intellectual property and technology transfer practices have made the HPV vaccine inaccessible in developing countries due to a suboptimal delivery system and high prices. Ad hoc solutions to improve access to the vaccine have been put in place, but these programs, which are essentially based on voluntary price reductions, do not address the systematic barriers to access. At present, despite the higher level of complexity involved in the production of vaccines, paths to production of follow-on vaccines could exist if a range of intellectual property, materials and know-how are made available to low-cost producers. Enabling production of follow-on vaccines that could attain regulatory approval via a parallel pathway to the demonstration of bioequivalence for small molecule generics would create greater efficiencies that could significantly reduce costs. Given the importance

⁹⁵ World Health Org. [WHO], Sixty-First World Health Assem. *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, WHA61.21, (May 24, 2008).

⁹⁶ X PRIZE Foundation Press Release, *X PRIZE Foundation to Help Fight Tuberculosis Worldwide with Gates Foundation Support*, Oct. 16, 2008, <http://www.xprize.org/foundation/press-release/x-prize-foundation-to-help-fight-tuberculosis-worldwide-with-gates-foundati>.

of universities in the production of the HPV vaccine and vaccines in general, universities must take proactive steps to ensure access through a Global Access Licensing policy. Adopting such a program could include a variety of currently available technology transfer mechanisms. In addition, universities should consider the concept of PMK pools to streamline availability of the resources needed to produce low-cost vaccines to be made available in developing countries. While there are a number of potential ways for universities to address the role of materials and know-how in enabling the cost-effective production of follow-on vaccines, the critical point is to recognize the necessity of addressing more than simply patents.