

**The Impact of Intellectual Property, University Licensing Practices, and
Technology Transfer on Regional Manufacturing of and Access to the HPV
Vaccine in Resource-Poor Regions**

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ACRONYMS USED

AUTM - Association of Technology Managers

CDC – Center for Disease Control and Prevention

CRADA – Cooperative Research and Development Agreement

DCVMs – Developing Country Vaccine Manufacturers

FCCC – Fox Chase Cancer Center

FDA – Food and Drug Administration

GAVI – Global Alliance for Vaccines and Immunisations

HPV – Human Papillomavirus

IP – Intellectual Property

IPA – Institutional Patent Agreement

IPO – Indian Patent Office

LMCs – Low- and middle-income countries

NIAID – National Institutes of Allergy and Infectious Diseases

NIH – National Institutes of Health

OECD – Organisation for Economic Cooperation and Development

PATH – Program for Access Technology and Health

PCT – Patent Cooperation Treaty

SEC – Securities and Exchange Commission

UNICEF - United Nations Children’s Fund

USPTO – United States Patent and Trademark Organization

VLPs – Virus Like Particles

WHO – World Health Organization

I. INTRODUCTION

Cervical cancer, the leading cause of female cancer mortality worldwide, disproportionately affects women in low- and middle-income countries (LMCs). Indeed, 89% of the estimated 492,000 new cases in 2002 occurred in the developing world.¹ Two new prophylactic vaccines, *Gardasil* from Merck and *Cervarix* from GSK, have proven effective at reducing Human Papillomavirus (HPV)-induced cervical lesions and some sequelae. Both vaccines protect against HPV-16 and -18, strains responsible for nearly 70% of cervical cancer incidence.² These vaccines could reduce deaths in LMCs with poor or non-existent cervical cancer screening programs. However, priced in private markets at a minimum of \$360 for the three-dose regimen,³ the vaccines remain largely inaccessible to those women who stand to benefit the most from vaccination. As a result, countless women die unnecessarily.

Christine Baze, a singer, songwriter, and band member, knew nothing about cervical cancer. She was unaware of the large role HPV played in its development, and she was blissfully ignorant of the purpose of the Pap smear test. All she knew was that making the annual trip to the gynecologist was a necessary evil. Then, in March of 2000, her doctor uttered the words that brought her world crashing down around her: at the tender age of thirty-one, she was diagnosed with cervical cancer. The result of unprotected sex with an HPV-infected partner prior to her college graduation, Baze never realized that having sexual intercourse just once was enough to contract the infection. Had she known, she would undoubtedly have taken more precautions to protect herself. Despite a valiant effort to keep her ovaries to preserve her fertility, she ultimately underwent both a radical hysterectomy and laparoscopic surgery in preparation for five weeks of

¹ Saxenian. 2007. IAVI.

² Agosti et al. 2007. NEJM.

³ Vaccines: VFC/CDC Vaccine Price List. 2009.

pelvic radiation, four rounds of chemotherapy, and three final rounds of internal radiation. As a result, her vagina became nothing more than a collection of raw nerves. In addition to her physical scars, she fell into severe depression and watched her marriage collapse as a result of the stigma associated with HPV.

The reality, however, is that Baze is lucky. While she was not well versed in the intricacies of HPV, the fact that she lives in the United States means her doctors certainly were. As a result, she gained access to life-saving treatment that allowed her to re-engage in life with renewed vigor. She may have paid a steep price – she will always bear the scars of her disease in that her infertility, her damaged intestines, bowel, and bladder, and her atrophied vagina can never be repaired⁴ – but ultimately, she is alive. Many women in the developing world are less fortunate. They fight a losing battle because they either lack access to cervical cancer screening or to cancer treatments or to both. The HPV vaccine promises to prevent this entirely as it has thus far proven safe and effective in preventing infection from HPV-16 and -18 and, as a result, more than half of known cervical cancer types. Achieving widespread access to it, however, is essential to fully realizing its life-saving potential.

The cervical cancer vaccine, however, is not the only vaccine that is inaccessible in the developing world. In addition to *Gardasil* and *Cervarix*, Hepatitis B and Rotavirus vaccines have been and continue to be underutilized in the developing world because of high private market prices. The diseases these two vaccines target disproportionately affect developing and underdeveloped nations. Indeed, 82% of fatal rotavirus cases in children⁵ and a majority of the 500,000 to 700,000 annual Hepatitis B-related deaths⁶ occur in resource-poor settings. The

⁴ Baze, et al. 2008. *Gynecologic Oncology*.

⁵ Parashar, et al. 2003. *Emerging Infectious Diseases*

⁶ PATH: Vaccine Resource Library. 2009.

successful development of new vaccines for these three diseases is therefore a welcome public health advance that can save many lives. The increasing technological complexity of these vaccines, however, requires intensive resources and investment for development that are principally available only to the private sector in developed countries. As western pharmaceutical companies are largely for-profit entities, they typically seek exclusive rights to patents protecting enabling technologies for drug and vaccine development in an effort to secure a return on their upfront costs. Consequently, market competition forces are stifled, and high drug and vaccine prices persist.

With the emergence of vaccine manufacturing sectors in several developing countries including India, regional manufacturers present an alternate production pathway for HPV vaccines that can offset the high prices of Merck and GSK's vaccines. Indeed, many regional manufacturers are now capable of producing vaccines similar to their imported counterparts at a fraction of the price. They are now routine suppliers of multiple vaccines to the United Nations Children's Fund (UNICEF) and the Global Alliance for Vaccines and Immunisation (GAVI).^{7,8} This new capacity coupled with viable markets for these products in the developing world suggests that developing country manufacturing may be key to improving LMC access to essential vaccines. However, these additions to the global vaccine development landscape are influencing the patent practices of western pharmaceutical companies. While these companies have traditionally not sought patents for their vaccines in LMCs, they are now making a concerted effort to do so as regional manufacturers threaten to share a portion of their profits. This raises questions about whether intellectual property promotes or constrains developing world vaccine access. Without the market exclusivity made possible by the patent licensing

⁷ Jodar et al. 2005.

⁸ GAVI Alliance Progress Report. 2007.

strategies that inventors employ, it would be difficult to find a pharmaceutical company willing to bring upstream drug and vaccine technologies to market. However, this market exclusivity may prevent regional manufacturers from making the HPV vaccine more affordable and therefore accessible in the developing world. Consequently, this vaccine may remain inaccessible in LMCs for decades despite the fact that their public health impact would be greatest in such populations.

As new vaccines increase in complexity, the ability of regional manufacturers to develop them will critically depend on access to technologies that may be protected by patents. Through three case studies on how technology transfer, patenting, and licensing practices impacted the development of HPV, Hepatitis B, and Rotavirus vaccines, I hope to explore how existing mechanisms can be harnessed to maximize the public health impact of new, essential vaccines. Many of the components that are arguably necessary to achieve and sustain widespread vaccine access already exist; the question now is how to capitalize on them in a manner that honors current intellectual property (IP) law, promotes further innovation, and enables vaccine affordability in LMCs.

II. LITERARY CONTEXT

Seven bodies of literature serve as a foundation for this study to assess the impact of patenting and licensing – and by extension, technology transfer – on access to HPV vaccines in LMCs. They include: (1) the importance of HPV vaccination, particularly in LMCs, (2) the science underlying the HPV, Hepatitis B, and Rotavirus vaccines, (3) the role of intellectual property in commercializing biomedical products like vaccines, (4) proposed patent licensing mechanisms for improving access to biomedical products and the limitations of these practices, (5) the importance and emergence of regional manufacturing to increase market competition, (6)

limitations of regional manufacturing, and (7) challenges despite low-cost regional manufacturing in improving access to vaccines in LMCs.

2.1. Cervical cancer: the need for vaccination

The United States and most developed countries have successfully lowered the cervical cancer incidence in their nations through effective screening programs.⁹ However, similar efforts have not been as successful in the developing world because such programs are largely absent or limited to urban areas.¹⁰ Though successful development of the two HPV vaccines is a step in the right direction, the \$360 price poses a significant barrier to the vaccination of 52 million 11-year-old girls in the developing world that stand to benefit most.¹¹ According to a recent cost-effectiveness analysis, to be cost-effective in middle-income countries, the vaccine cannot exceed \$5 per dose. Furthermore, to maximize affordability and cost-effectiveness in countries with less than \$1000 in per capita GDP, the vaccine can only cost \$1-2 per dose.¹² The price per dose must therefore fall dramatically to maximize the global benefit of the vaccine. Past experience with introduction of new vaccines like the Hepatitis B vaccine, however, suggests that 20 years could elapse before women in the poorest regions gain access to HPV vaccines.¹³ Meanwhile, every five-year delay in vaccine introduction could result in nearly 1.5 to 2 million more HPV related deaths.¹⁴

Merck and GSK might choose to facilitate vaccine access in LMCs through tiered pricing programs that differentially lower HPV vaccine prices in low-income markets. The affordability of currently available HPV vaccines can also be facilitated in 2 others ways: (1) Merck and GSK

⁹ Gakidou, Nordhagen et al. 2008. PLoS.

¹⁰ Cervical Cancer Screening in Developing Countries.

¹¹ Saxenian. 2007. IAVI.

¹² Agosti et al. 2007. NEJM.

¹³ Kane et al. 2006. Vaccine

¹⁴ Agosti et al. 2007. NEJM.

can donate vaccines to the lowest-income markets, and (2) the Global Alliance for Vaccines and Immunisations (GAVI – a global health partnership that increases access to existing vaccines, strengthens health systems around the world, and introduces new immunization technologies) can procure vaccines at lower cost for distribution in low-income regions. Vaccine donations and/or subsidies from the GAVI Alliance and the Bill and Melinda Gates Foundation can solve access issues by partially offsetting the gap between the currently high market price and the target price range needed for cost-effectiveness and affordability and consequently, broad access. As a last resort, governments can exercise their monopsony power – that allows them to capitalize on their ability to control market entry – and set low prices.

The above mechanisms, though all implemented to a certain degree, are unsustainable in the long term. While Merck and GSK may offer discounted HPV vaccine prices for developing world use, it is unlikely that these reduced prices will come close to meeting affordability targets given the high cost of producing current generation vaccines. Consequently, vaccine donations, subsidies, tiered pricing efforts, and other voluntary price reduction strategies may be insufficient to achieve long term, widespread access. In addition, GAVI faces a \$4 billion shortfall and is unlikely to subsidize HPV vaccines in the near future. It is therefore imperative to explore other mechanisms like regional manufacturing to reduce and sustain low prices.

2.2. Scientific background for HPV, Hepatitis B, and Rotavirus vaccines

Understanding the science behind these vaccines is essential to determining whether the underlying technology poses a barrier to regional manufacturing of low-cost vaccines. Indeed, only with knowledge of the science can one conduct a critical assessment of what the patents for these vaccines claim. As further discussed in Chapter 5, this analysis will be critical in the effort

to identify whether developing country vaccine manufacturers (DCVMs) – can work around existing patents using alternate technologies.

2.2.1 HPV vaccines

Currently marketed HPV vaccines *Gardasil* and *Cervarix* are two of the most complex recombinant vaccines developed to date. They entailed at least fifteen years of research and development. These vaccines are both composed of virus like particles (VLPs) that are empty virus shells that lack the genes responsible for making HPV so virulent. Both Gardasil and Cervarix have VLPs assembled from the L1 HPV antigen, a molecule that is found on the outer shell of the virus and has been shown to be highly immunogenic. They specifically contain VLPs from two strains of the L1 HPV antigen: HPV-16 and -18, which are known to cause over 70% of cervical cancer cases worldwide. The method of purifying VLPs and producing high enough yields to make large-scale vaccine production possible is very difficult. To date, no alternate method of producing and expressing them has been as successful as the process described and protected in both Merck and GSK's patents and their proprietary knowledge.¹⁵

2.2.2 Rotavirus vaccines

The rotavirus vaccine uses a live attenuated virus that is repeatedly passaged (or made less virulent) in the African Green Monkey kidney cell line – an unnatural host cell – by infecting it with a rotavirus repeatedly until the virulence of the virus strain in the cell diminishes. Once attenuated, the virus can be introduced into human patients to induce an immune response without infecting them with the virus itself. There are two methods of attenuating a virus: (1) manipulation by passaging in cell lines, or (2) mixing up the virus's genes with those of other species. This latter process results in what is called a reassortant virus, which

¹⁵ Crager et al. 2009. AJLM.

comprises the underlying technology behind both Merck's vaccine, Rotateq, and the National Institute of Health (NIH)'s vaccine candidate. To produce these live attenuated virus vaccines, developers must have access both to the particular strain of virus (biological materials) and the methodology (typically the particular cell line that works best) to produce a marketable product.¹⁶

2.2.3 Hepatitis B vaccines

The Hepatitis B vaccine employs recombinant DNA (which means combining genes from different organisms) technology. This involves using molecular biology techniques to produce large quantities of any protein in vitro starting from the DNA sequence. The Hepatitis B vaccine was developed using the Hepatitis B surface antigen, which has been shown to induce a strong immune response without exposing the recipient of the vaccine to the virus itself. Originally, this antigen was isolated from the blood plasma of those testing positive for the virus. However, recombinant mechanisms have made it possible to express the DNA sequence of the surface antigen and to produce it in mass quantities in the laboratory by inserting the artificially synthesized gene into rapidly reproducing bacteria or yeast.^{17, 18, 19}

2.3. Intellectual property key to commercializing vaccines globally

The technologies underlying all three vaccines required great development efforts and are therefore patented. The patent system was originally developed to reward inventors who had expended great financial and human capital to contribute to society's collective knowledge. The driving force of the system was the idea that awarding short-term monopolies to inventors would

¹⁶ Dennehy. 2008. Clinical Microbiology Reviews.

¹⁷ Hilleman. 2000. Vaccine.

¹⁸ Patlak. Hepatitis B Story.

¹⁹ Vaccine History. Hepatitis B Vaccine Foundation.

allow them to recoup their investments through market exclusivity.²⁰ The disclosure of their inventions could also be used to stimulate future innovation.²¹ However, though the motives behind the system are pure, it was developed prior to the explosion of the biomedical industry. As a result, the importance of rapid access to life saving inventions was not widely appreciated. Provisions for immediate, widespread use of such innovations were therefore not built into the system. The monopolies patents grant have therefore threatened to impede access to essential medicines in certain instances, the most prominent of which is the case of antiretrovirals in Africa.²²

Intellectual property (IP) facilitates the development of products or services by conferring patent rights to entities who have the capacity and ability to develop such products for the market. These rights are granted through a contract called a license. In return for granting access to the patent rights, the patent owner receives remunerations from the licensee, often called royalties, following the sale of the products or services. Typically, there are two types of licenses that are awarded to enable commercialization of biomedical products such as vaccines: (1) exclusive licenses, and (2) non-exclusive licenses. Exclusive licensing of patents grants commercial entities sole rights to the patent-protected technologies in addition to transferring to the licensee a market monopoly initially awarded to the inventor. Consequently, companies can often expect to have between 15 and 17 years of market exclusivity in which to develop and sell their vaccines before facing competition. In contrast, non-exclusive licenses grant multiple companies the rights to protected technologies, thus allowing several entities to bring similar products to market. However, although non-exclusive licenses can promote availability of low-

²⁰ Mossoff. 2001. *Hastings Law Review*.

²¹ Fromer. 2009. *Iowa Law Review*.

²² Kapczynski et al. 2003. *Science*.

cost products through market competition, they may also reduce financial incentives for the development of products that require significant commercial investment. Because companies assume a great deal of risk when they license upstream biomedical technologies, they require a guarantee of a full return on investments. They may therefore be more hesitant to work with candidates for which there is the potential for immediate market competition. As a result, companies today often prefer to seek exclusive licenses to patent rights for biomedical product development.

2.3.1 Bayh-Dole Act of 1980

Prior to 1980, non-exclusive licenses were the main method in which technology was transferred from universities and non-profits to the pharmaceutical and biotechnology industries (with the exception of small-molecule drugs developed through Institutional Patent Agreements (IPAs)). While most enabling vaccine technologies were developed in university and non-profit research laboratories using federal funding in the past, the government differed from present practices in that it retained, by default, ownership of innovations resulting from federal funding (except in cases covered by IPAs) and generally offered only non-exclusive licenses to commercial entities. Pharmaceutical companies were therefore hesitant to invest in and develop vaccines given that other companies could acquire licenses to the same technology and develop similar products. The benefits taxpayers saw from their support of federal research endeavors were thus limited. The Bayh-Dole Act was passed in 1980 with the hope of improving the public benefit from biomedical research especially. It sought to boost commercialization of research conducted by universities and non-profits by allowing them to retain ownership of innovations through patent rights and to exclusively license them to commercial entities if necessary for product development.

In the years since, the biotechnology industry has experienced dramatic growth, especially as universities and non-profit organizations have created technology transfer offices to facilitate licensure of patents to pharmaceutical and biotechnology companies. Indeed, there has been a ten-fold increase in the number of universities actively engaging in patenting and licensing of technologies since 1980 when only about 25 to 30 institutions were involved.²³ Furthermore, a 1997 survey conducted by the Association of Technology Managers (AUTM) indicates that 70% of the active licenses that responders held are in the life sciences (a field that produces both products and methods to diagnose disease, minimize pain and suffering, and save lives).²⁴

Many experts therefore view the Bayh-Dole Act as a success because of how it melded the interests of the government, academia, and industry to foster the development of drugs and vaccines with the potential to save many lives.²⁵ Critics of Bayh-Dole, however, emphasize that a majority of the 28,000 government-held, unlicensed patents in 1980 were patents that companies had declined to license altogether.²⁶ These experts further assert that many of the technologies that were developed into marketable products through exclusive licenses following Bayh-Dole could have been similarly disseminated and developed either by being placed in the public domain or by being non-exclusively licensed to commercial entities.²⁷ The extent to which Bayh-Dole facilitated biomedical product development is therefore debatable. However, the exclusive licensing practices it promoted have certainly changed the way biomedical products are developed and marketed.

²³ Eisenberg. 1996. Va. L. Rev.

²⁴ FY 1997 Licensing Survey.

²⁵ COGR. The Bayh-Dole Act.

²⁶ Eisenberg. 1996. Va. L. Rev.

²⁷ So et al. 2008. PLoS Biology.

2.3.2 Stevenson-Wydler Act

The Bayh-Dole Act, however, was not the only piece of legislation to jumpstart the more widespread commercialization of enabling technologies for essential medicines. The Stevenson-Wydler Act, also passed in 1980, is a functional equivalent, determining instead how patents on technologies developed directly by government researchers are licensed. The government claims ownership of all innovations resulting from federally funded research at the National Institutes of Health (NIH), the Center for Disease Control and Prevention (CDC), and the Department of Energy, among others. The Act's fundamental purpose is to make the results of government research efforts widely available and beneficial to society through the establishment of technology transfer programs in each laboratory. Each research project must be evaluated by technology transfer personnel to determine its applicability to the general public. Those projects with the potential to enhance the public good are then licensed to an industry partner for product development and marketing. Government-run laboratories now also grant exclusive licenses to pharmaceutical and biotechnology companies in those instances when exclusivity is deemed the best way to see a tangible benefit from that research.²⁸

However, while the Stevenson-Wydler and Bayh-Dole Acts may have enabled the development and marketing of more products, affordability was not always an explicit goal. Indeed, the NIH prefers to use non-exclusive licensing to disseminate technologies that could have a great public health impact, yet they do not make product affordability a condition of their licensing agreements.²⁹ This is particularly apparent when looking at the global access disparity for biomedical products.

²⁸ Linsteadt et al. 1981. *Journal of Technology Transfer*.

²⁹ Personal Interview With Dr. Albert Kapikian and Dr. Mukul Ranjan. 2009.

2.4. Licensing mechanisms to offset gap between current and target vaccine prices and their limitations

Several proposed licensing models may be effective in removing patent-created barriers and increasing affordability and access in LMCs.

1. Negotiated license: Patent owners license their technology to producers in target regions for distribution who commit to selling versions of the product at discounted prices.³⁰
2. Equitable Access License: This applies to any innovations produced through university research and promotes non-exclusive licensing of fully developed drugs and vaccines to developing country biotechnology companies. It is particularly useful for upstream technologies such as those used in developing the HPV vaccine.³¹
3. Compulsory license: Governments permit development and marketing of patent-protected drugs and vaccines without the permission of the patent owner in their countries.³²

In addition, Outterson of Boston University School of Law and Aaron Kesselheim of Harvard University proposed a new avenue to improve affordability.³³ Unlike the previous four mechanisms, however, it has not been tried in practice.

Outterson separately proposed a patent buy-out model to facilitate developing country access to essential drugs and vaccines. The initiative proposes the sale of the intellectual property and exclusive marketing rights in the developing world to governments, inter-governmental organizations (World Health Organization – WHO, United Nations, World Trade Organization,

³⁰ Outterson et al. 2008. Health Affairs.

³¹ Chokshi et al. 2007. JAMA

³² Maybarduk et al. 2009. AJLM.

³³ Outterson et al. 2008. Health Affairs

etc.), and/or foundation donors to enable regional manufacturers to develop and sell drugs and vaccines at greatly reduced prices. For a price approximately equaling the seller's forgone recoupment of R&D expenditures, purchasers will be permitted to offer non-exclusive, royalty-free licenses to viable developing country manufacturers. Patent buy-outs would protect the right of pharmaceutical companies to recoup their R&D investments while simultaneously promoting the maximization of public health benefits through widespread access to affordable biomedical products.³⁴

Additionally, Outterson and Kesselheim suggested a Generic Open (GO) License model that would immediately make drug and vaccine technology available to regional manufacturers. Efforts to develop and market generic versions of patented pharmaceuticals could begin quickly, eliminating some detrimental effects that twenty-year monopolies for patented products have on accessibility and further innovation. Outterson et al. proposed that GO License fees be roughly equivalent to the portion of profits from developing world sales that pharmaceutical companies would put towards future R&D.³⁵

While negotiated licenses, the GO License, the Equitable Access License, and Outterson and Kesselheim's suggestions may partially increase access to *Gardasil* and *Cervarix* in the short term, they depend entirely on voluntary participation by pharmaceutical companies. In addition, as pathways like Outterson's Patent Buy-Out model are dependent on financing from philanthropies and public health organizations, they cannot be sustained indefinitely; philanthropic funding capacity is necessarily limited.

Finally, compulsory licenses, while a powerful tool, are rarely used and as such are not likely to be implemented unless the country sees cervical cancer as a severe public health

³⁴ Outterson. 2006. AJLM.

³⁵ Outterson et al. 2008. Health Affairs

condition. In countries that suffer from high burdens of malaria and AIDS, cervical cancer – which only affects women and is less common than those other diseases – is less likely to be seen as a public health threat sufficient to require invoking such a drastic measure.

2.5. Market competition a viable alternative to increasing vaccine affordability

Developing country pharmaceutical companies have proven that they have an increased ability to produce biomedical products, especially generic versions of pharmaceutical drugs. In the last two decades, they have also demonstrated a growing capacity for the biotechnology necessary to make biologicals like vaccines. Most notable, however, is that developing country vaccine manufacturers (DCVMs) have been able to break into these markets while maintaining affordable prices for their drugs and vaccines. For instance, they have significantly reduced prices for several drugs, including antiretrovirals,³⁶ and have also been successful in producing high quality, low-cost vaccines for global, low-income markets.

Through their examination of recombinant Hepatitis B vaccine manufacturing specifically, Kane et al. indicate that market competition made possible by DCVMs dramatically reduced vaccine prices to meet established cost-effectiveness and affordability targets. Indeed, while many industrialized countries licensed the Hepatitis B vaccine in 1981, much of the developing world did not gain access until the late 1990s when a number of DCVMs launched their indigenously developed vaccines.³⁷ The ensuing market competition caused vaccine prices to drop from \$100 per dose in 1980 to \$0.25 in 2006.³⁸ The price reduction also reduced costs for governments and international agencies procuring these vaccines.³⁹ Harnessing regional

³⁶ “Aids, Drug Prices, and Generic Drugs.” 2009.

³⁷ Kane et al. 2006. Vaccine

³⁸ PATH. 2009.

³⁹ GAVI Alliance Progress Report. 2007.

manufacturing capacity to increase market competition may therefore be a viable mechanism to reduce HPV vaccine prices to affordable levels globally.

2.6. Criticisms of regional manufacturing

Regional manufacturing, however, has its critics. Despite the eight Indian vaccine manufacturing companies developing vaccines ranging from Hepatitis B to Japanese encephalitis, the industry to date has largely confined itself to producing different versions of already marketed vaccines using slightly different production processes. Only recently have these companies engaged in novel vaccine development. Frew et al. discuss how this can be in part attributed to a shortage of advanced training programs and a scarcity of qualified personnel to give India's biotechnology sector a strong international presence. As many talented scientists and students have left the country in search of more lucrative opportunities abroad, only a limited number of researchers remain with the training necessary to be successful in cutting edge biotechnology. Critics argue that regional manufacturers must gain expertise as biological investigators to produce vaccines for the global market. While these assessments are partially true, such shortcomings can be remedied. Indeed, with companies such as Novartis opening research centers in India, the "brain drain" may diminish, giving the country increased access to essential human capital.⁴⁰ Furthermore, as Chokshi and Kesselheim discuss, use of technology transfer programs to build capacity in the developing world vaccine manufacturing industry can stimulate a new sector of the economy to engage in high quality, low cost vaccine development.⁴¹ India especially has manufacturing companies that continuously seek to scale up their biotechnology expertise, and with assistance from western universities and/or non-profit research institutions, they can do so. As successful regional manufacturing can be made possible

⁴⁰ Frew et al. 2007. Nature Biotechnology.

⁴¹ Chokshi et al. 2009. British Medical Journal.

through technology transfer, universities in the developed world are in a unique position to facilitate capacity building in biomedical research through collaborative partnerships and training programs.

Critics also worry about the role regional manufacturing will have in fostering the “gray market” of drugs and vaccines. As Outterson and Smith describe, with the advent of online consumer drug purchasing, there is increased opportunity for low-cost drugs and vaccines produced in the developing world to be resold in industrialized countries at the developed world price. The US Food and Drug Administration (FDA) estimates that 1% of drugs on the market are counterfeit. The Deputy Secretary General of the Council of Europe believes 8% to 10% of the European pharmaceutical market is composed of counterfeit drugs and vaccines. Pharmaceutical markets in some countries may be composed of as much as 12% of counterfeit products.⁴² While gray markets, unlike black markets, are not considered illegal because the goods passing through them are genuinely manufactured, those who sell gray market goods are not authorized by patent and/or trademark holders to do so.⁴³ Critics believe that enabling regional manufacturing of low-cost drugs and vaccines alongside traditional western pharmaceutical development may render impossible the ability to control the inflow and outflow of pharmaceutical products through the gray market.

The sustainability of this gray market is necessarily limited, however, because the FDA – among other pharmaceutical regulators – is employing new technology to manage the flow of pharmaceutical products. Specific strategies include embedding product codes and/or codes specific to individual pharmaceutical companies into the packaging paper to allow regulators to

⁴² Outterson et al. 2006. Albany Law Journal of Science and Technology.

⁴³ Chen. Atlantic Economic Journal. 2002.

trace drugs and vaccines to their production sources.⁴⁴ Variations in product packaging can allow distributors globally to distinguish between products produced specifically for the developing world and those developed for other regions.

2.7. Limitations despite regional manufacturing

It is important to note that even if regional manufacturing – facilitated by revised patent licensing practices and subsequently increased sharing of materials and know how – is successful, it will not single-handedly improve access to vaccines. The HPV vaccine currently on the market has fundamental weaknesses for achieving widespread access that will be difficult to overcome during implementation in LMCs. As Schiller and Nardelli state in their defense of the need for second-generation HPV vaccines, the current vaccine requires refrigeration during transport and a series of three intramuscular needle injections over the course of six months. Even if regional manufacturers could develop an affordable version of *Gardasil* or *Cervarix*, it is questionable whether LMCs have access to refrigerated trucks, usable roads, and an army of health professionals with the capacity to reach the millions of young women and girls living in rural areas three times in a six-month period. With frequent comparisons made between the Hepatitis B vaccine and the current first-generation HPV vaccine, it is appropriate for Schiller et al. to note that the successful 100-fold price reduction for the former (mostly due to regional manufacturing) coupled with some concerted implementation efforts in the developing world has not resulted in widespread vaccination. Indeed, as the Hepatitis B vaccine also requires three intramuscular injections, it has been underutilized in the developing world.⁴⁵ Unless the developing world can successfully overcome these challenges, it is likely that *Gardasil*, *Cervarix*, and generic versions thereof will have only a limited effect on global health.

⁴⁴ Combating Counterfeit Drugs: A Report of the Food and Drug Administration. 2004.

⁴⁵ Schiller et al. 2006. Vaccine.

Furthermore, even if technical and infrastructural challenges can be resolved, HPV vaccine acceptability is crucial to achieving widespread vaccination. In recounting a HPV vaccination acceptability study in the United States, Zimet highlights that prior to reading a pre-prepared information sheet, 55% of parents were in favor of vaccinating their children, 23% were opposed, and 22% were undecided. After learning more about HPV and HPV vaccination, vaccine acceptability rose to 75%, with 65% of undecided parents shifting to a favorable position regarding vaccination. It appears that in all studies Zimet describes, parents were more concerned about protecting the health of their children than they were about promoting sexually risky behavior. While such open-mindedness is promising, no published study discusses how those in culturally and religiously conservative societies view vaccination against a sexually transmitted infection.⁴⁶ In many of these countries, premarital sex is viewed as taboo and many parents refuse to contemplate the idea that their children might willingly or unwillingly stray from family values. Furthermore, as HPV generally does not turn into a serious health problem until later in life, many families with more immediate health concerns may be hard pressed to prevent a problem that likely will not show symptoms for decades. It is therefore possible that efforts to reduce HPV vaccine prices through regional manufacturing may not improve public health outcomes in the developing world because cost is not the only determinant of use. The Program for Access Technology and Health (PATH) is, however, addressing concerns of implementation and acceptability in the developing world through demonstration projects. Four such trials are underway in India, Peru, Uganda, and Vietnam.⁴⁷ These programs have been supported through donations of Gardasil from Merck.⁴⁸

⁴⁶ Zimet. 2005. *Journal of Adolescent Health*.

⁴⁷ PATH: *Cervical Cancer Vaccine*. 2009.

⁴⁸ Merck & Co. 2009.

Despite its potential limitations and the validity of critics' concerns, regional manufacturers are in a position to address some of these challenges. Indeed, they develop vaccines with existing infrastructure constraints in mind. Specifically, given the difficulties associated with cold storage transportation, they can focus their vaccine development efforts on technologies that render refrigeration unnecessary. Furthermore, they can implement new vaccines using existing distribution infrastructures such as the Abhay Clinics (affiliated with Indian Immunologicals – a vaccine manufacturing company in Hyderabad, India), which are equipped to oversee vaccination programs among the poor.⁴⁹ Furthermore, these manufacturers could develop formulations of vaccines containing combinations of already-delivered childhood vaccines that may facilitate more widespread implementation. Indigenously developed vaccines may also increase acceptability among potential vaccine recipients. While these benefits certainly do not solve all of the problems, if the affordability of HPV vaccines can increase the number of people accessing it, it is a risk worth taking.

III. RESEARCH DESIGN / METHODOLOGY

The goal of this project is to determine if there is a method for licensing intellectual property that best enables market competition through regional manufacturing. I have therefore constructed two case studies on the Rotavirus and Hepatitis B vaccines in India in addition to the one on HPV. These two vaccines were chosen because: (1) they also target conditions that disproportionately affect LMCs, (2) they were similarly developed by large pharmaceutical companies and were first marketed only in OECD countries, (3) university-based research and IP were important for the commercialization of these vaccines, and (4) the licenses that academic

⁴⁹ Personal Interview with Indian Immunologicals. 2007.

and non-profit institutions used to disseminate key technologies differ from those used for HPV vaccines.

The HPV, Hepatitis B, and Rotavirus vaccines each occupy a different position in the licensing spectrum. While the HPV vaccine was developed using exclusive licenses, the Rotavirus vaccine technology has been non-exclusively licensed to regional manufacturers in India and the Hepatitis B vaccine involved minimal licensing altogether as regional manufacturing of the vaccine occurred following the expiration of key patents. Exclusive licenses (under which the licensee has sole right to produce and market a product using patented technology) and non-exclusive licenses (which allow multiple entities to use protected technology for product development) are two realistic alternatives to the licensing mechanism proposals described in the literature review. Indeed, to date, either exclusive or non-exclusive licenses have been issued in bringing every vaccine to market for the first time. Granting either exclusive or non-exclusive licenses to companies in developing countries could be a potential solution as regional manufacturing becomes an increasingly viable alternative.

Licensing technology from developed country research institutions and engaging in technology transfer partnerships with licensors (those who license technology) can help regional manufacturers gain access to the IP and know-how they require. However, knowing what technologies are available for licensing is difficult. Other than the NIH, most universities are not required to publicize the issuance of exclusive or non-exclusive licenses. Licensors need only divulge specific terms and fees related to their licensing agreements to the Securities and Exchange Commission (SEC) if they are publicly traded companies. These documents can be difficult to access and comprehend especially outside the United States. Identifying specific licensing terms can therefore be a challenge. As it is imperative for regional manufacturers to

know what technologies are available for licensing, I have combed through SEC filings in an attempt to identify the types of agreements made for each of the vaccines I have analyzed in this study. This information has been supplemented by voluntary disclosures by the researchers and/or technology transfer professionals involved in the contracts. To confirm that my interpretation of the documents is correct, I have verified my understanding of the licensing information I discovered in the SEC filings with many of those who were directly involved in writing the contracts.

3.1. From patents to licensing

A cross comparison of the licensing histories of the HPV, Hepatitis B, and Rotavirus vaccines can inform the debate about which existing type of licensing would best enable regional manufacturing and market competition while still honoring intellectual property law. As licenses are only necessary when patents covering the desired technology exist, I have constructed patent landscapes for the HPV and Rotavirus vaccines to gauge the role patents have played, if any, in enabling or inhibiting efforts of regional vaccine manufacturers. (A similar landscape for Hepatitis B vaccines was not assembled because regionally manufactured versions were developed and marketed only after patent expiration. Therefore, patents did not inhibit any regional manufacturing efforts for this vaccine.) The root of the availability and accessibility problem in the developing world lies in where universities and pharmaceutical companies originally filed for and received patents. By constructing patent landscapes for the two vaccines, I can assess (1) what types of patents each non-profit and for-profit institution owns and (2) how those patents have and will continue to impact regional manufacturing. As a result, I can better determine whether and what types of licensing will be necessary to achieve widespread developing world vaccine access. Identifying whether patents covering key HPV and Rotavirus

vaccine technologies exist in all developing countries with regional manufacturing capacity would have been ideal. However, a lack of electronic databases in which the full text and claims of patents and pending applications are published as well as limited English language resources for several LMCs posed technical barriers. I therefore restricted this analysis to the role of patents and licenses on regional manufacturing in India.

India is an apt example as it bears a 25% cervical cancer burden and 17% of the global rotavirus burden.⁵⁰ Furthermore, 10% of annual Hepatitis B-related deaths globally occur in India⁵¹ (data for the percentage of global HBV incidence in the country is unavailable). The country therefore has an incentive to ensure HPV, Hepatitis B, and Rotavirus vaccine affordability. Furthermore, it possesses a robust vaccine industry with the capacity to produce high quality vaccines. The presence of a large national market provides additional motivation for developing country vaccine manufacturing companies to invest. Finally, the global need for low-cost HPV, Hepatitis B, and Rotavirus vaccines offers the potential to expand their markets to include other low-income regions such as Africa and Southeast Asia. Past experience with Hepatitis B vaccine production serves as precedent for the important role India plays in the vaccine development landscape. Specifically, seven Indian companies entered the market with high quality vaccines that drove down prices in the last decade.⁵² This resulted in a dramatic increase in Hepatitis B vaccine accessibility both in India and abroad. Barring intellectual property and know-how obstacles, there is reason to believe that they can achieve similar success with HPV and Rotavirus vaccines.

3.2. Generating patent landscapes for HPV, Hepatitis B, and Rotavirus in US and India

⁵⁰ Sharma et al. 2008. Journal of Clinical Microbiology.

⁵¹ Introducing Hepatitis B Vaccines.

⁵² Frew et al. 2006. Nature Biotech.

First, using scientific literature and scientific trade publications, I identified which academic, non-profit and for-profit institutions were primarily involved in the research, development and commercialization of each vaccine. This helped me identify the names of institutions that own (“assignee”) relevant intellectual property and the names of the “inventors.” I then interviewed inventors and technology transfer professionals to gain a basic understanding of the patenting and licensing strategies employed by the key institutions involved in initial vaccine development. Subsequently, when constructing the patent landscapes, I identified the broad “universe” of patents for each vaccine by constructing search algorithms that were used to query the Delphion™ Patent Database (available from *Thomson Scientific*). For example, the search query below identified all US and international patent filings that contain the following search terms in the Claims field of the patent.

Query: (“papillomavirus” OR “HPV”) AND “vaccine” IN <Claims>

I also used “assignee” and “inventor” names identified through the literature review as search terms to also find relevant US and international (Patent Cooperation Treaty) patent filings. In addition, I used Derwent Patent Index to identify whether corresponding patents have entered the national phase in other countries (meaning whether inventors have filed for patents in specific countries following the thirty month period in which the application is verified as complying with the Patent Cooperation Treaty), particularly countries that are classified as low- or middle-income countries.⁵³

As a growing force in the vaccine market because of their increased technological capacity, developing country vaccine manufacturers will likely face increasing intellectual property restrictions from pharmaceutical companies seeking to use patents to stem competition.

⁵³ I had access to Delphion through Dr. Cook-Deegan’s Center and got access to the Derwent Patent Index through my Public Policy Studies internship at the Initiative for Medicines, Access, and Knowledge.

Consequently, they may be prevented from producing some of the more complex vaccines like *Gardasil*. In this context, manufacturers – who are often unaware of intellectual property barriers due to limited resources – will need to know the extent to which they have the freedom to develop alternate vaccines. To determine whether patents identified through Delphion and Derwent Patent Index have been filed and perhaps even granted in India, I used the publicly available Big Patents and Indian Patent Office databases.⁵⁴

Often, however, when looking at patents, it was still difficult to comprehend what they meant for regional vaccine development and how the licensing practices used to disseminate these protected technologies to the pharmaceutical industry might either assist or constrict developing country manufacturing capacity. To ensure that the patents I ultimately included are of relevance to my thesis, I read the claims in both patent applications and granted patents, looking for language that indicated protection of either processes for producing vaccines or the vaccines themselves. In this way, I was better able to assess the impact different types of patents and applicants might have on regional manufacturing efforts.

Placing the intellectual property for each vaccine in the context of its licensing history has shed light on how university patenting and licensing practices have promoted or constrained developing world manufacturing of these vaccines.

3.3. Identifying barriers other than intellectual property to regional manufacturing

Vaccines differ from generic drug manufacturing in that the latter utilizes alternate processes to develop the same compound. In the case of vaccines, alternate processes will yield slightly different vaccine compositions at best. As a result, all new vaccines will have to undergo safety and efficacy clinical trials to be approved by regulatory agencies globally. There are three

⁵⁴ Big Patents Database is a publicly available resource. My Public Policy internship supervisor helped me access the Indian Patent Office database.

phases of clinical trials: Phase 1, which are safety trials, Phase 2, which are efficacy trials, and Phase 3, which involves further efficacy trials in larger samples. Most clinical trials are expensive and have historically been funded only by governments or multinational pharmaceutical companies. More importantly, vaccine manufacturers will also require access to specific biological materials and know-how required for scaling up production of their vaccines to bring what many refer to as “bio-similar vaccines” to market. Identifying which patents are granted or are pending in India is therefore only the first step in assessing barriers to vaccine development.

I needed to identify what biological materials, technologies and know-how are required for each specific vaccine and whether regional manufacturers faced constraints in accessing them. I also needed to assess if regional manufacturers had the capacity to fund and conduct clinical trials required for regulatory approval of their vaccines. I therefore interviewed researchers and technology transfer professionals at universities and non-profits and at regional manufacturing companies in India to understand the specific challenges regional manufacturers have faced with respect to vaccine development. I specifically interviewed key personnel at Bharath Biotech, Shantha Biotech, Serum Institute of India, and Indian Immunologicals as part of two field trips, the first in December 2007 and the second in July 2009. These four manufacturers were involved in developing at least two of the three vaccines I studied. They were therefore able to offer a unique perspective on how the presence of patents and access to biological materials and know-how barriers affect their ability to develop these three vaccines.

IV. Case Studies

Each sub-section in this chapter will provide a look at the development and licensing history for the HPV, Rotavirus, and Hepatitis B vaccines, respectively, to give a sense of which

players were responsible for bringing the vaccines to market. This context will provide a better understanding of the complexities of patenting and licensing and will illuminate the impediments patents can become to vaccine development and access. An analysis of each vaccine's IP landscape will then directly discuss the role patents have in facilitating regional manufacturing efforts in India and will conclude with an assessment of how the type of licenses used to disseminate technology may have influenced the capacity and speed with which DCVMs have been able to develop novel and/or generic products.

4.1 HPV VACCINES: FROM DEVELOPMENT TO LICENSING

The intellectual property history for the HPV vaccine is complex and is the topic of much debate. Enabling technologies for the vaccines (composed of HPV-L1 major capsid antigen virus-like particles (VLPs) that prevent persistent infection from HPV-16 and -18 (strains that cause nearly 70% of cervical cancers) originated from independent research efforts at the University of Queensland (Australia), Georgetown University, the National Cancer Institute (NCI, USA), and the University of Rochester. These institutions filed patents claiming similar technologies on July 19, 1991, June 25, 1992,⁵⁵ September 3, 1992, and March 9, 1993⁵⁶ respectively (Appendix 3). As the United States Patent and Trademark Organization (USPTO) determines patent ownership based on who invented the technology first (otherwise known as a first to invent system) as opposed to who filed an application first (a first to file system that is widely used in international jurisdictions including the European Union), six two-way interferences⁵⁷ were declared on October 21, 2001⁵⁸ to determine who developed the technology

⁵⁵ CAFC: Schlegel v. Frazer. 2007.

⁵⁶ USPTO Patent Application Information Retrieval.

⁵⁷ A patent interference is an administrative proceeding in which a panel of judges of the United States Patent and Trademark Office attempt to determine which applicant is entitled to the patent

first and therefore deserved priority. Georgetown was awarded priority for the VLP-based technology on September 20, 2005.⁵⁹ However, because Georgetown researchers did not claim a method of producing and purifying VLPs for vaccine development in their patent application, researchers at the University of Queensland (who had filed first and had claimed such a method) filed an appeal with the USPTO on December 29, 2005.⁶⁰ The Court of Appeals of the Federal Circuit overturned the initial USPTO decision and instead granted priority to Queensland on August 20, 2007.⁶¹

In the midst of this patent struggle, Merck and GSK (which received some of its rights to the HPV vaccine technology from a worldwide alliance it finalized with MedImmune on January 16, 1998⁶²) cross-licensed their respective HPV vaccine IP holdings. As each had exclusively licensed technology from different institutions involved in the interferences to enable vaccine development and marketing, they sought to ensure continued market exclusivity and freedom to operate following the resolution of the interferences. As they developed their own products – *Gardasil* (Merck) and *Cervarix* (GSK) – they too filed for and received patents.

Consequently, with the patenting activity from the four academic research institutions, Merck, GSK, along with other universities and non-profits worldwide, the IP landscape for HPV vaccines is complex, with 81 US patents granted to date, corresponding to 86 Patent Cooperation Treaty (PCT) applications. 18 entities – 10 of which are non-profit – own these US patents. Non-profits own 20 of the 81 US patents, for-profits own 55, and for-profit and non-profit entities

if the technology is claimed in two or more pending applications or at least one pending patent application and one patent issued within one year of the pending application's filing date.

⁵⁸ USPTO Patent Application Information Retrieval. Application No. 08/185/928.

⁵⁹ USPTO Patent Application Information Retrieval. Application No. 08/185/928.

⁶⁰ "Personal Inquiry with CAFC." Telephone interview. 26 Aug. 2009.

⁶¹ CAFC: Schlegel v. Frazer. 2007.

⁶² Billich. 2003. Current Opinion in Investigational Drugs.

jointly own 6 (Appendix 3). Merck owns the most patents, 24, followed by GSK and the US Government (arising from the NCI), with 8 patents each.

The landscape makes very clear that Merck and GSK have exclusive control of both the key first generation HPV vaccine technology as well as the HPV vaccine product as a whole in the US and other Organisation for Economic Cooperation and Development (OECD) countries (essentially, developed nations in North America and Western Europe). Because Merck and GSK obtained exclusive licenses to the enabling technology and have filed and received subsequent patents on production methods, nucleic acids of viral L1 proteins, and even the product altogether, no other companies in the developed world can produce HPV vaccines that use the VLP technology until these patents expire. The resulting lack of market competition has prevented the vaccine's high price from falling, making it unaffordable in a majority of low-income countries. Regional manufacturing of a high quality, low cost HPV vaccine, however, could enable more widespread access. Yet, little is actually known about whether HPV vaccines and their underlying technology have been patented in LMCs, especially in developing countries that could bring competitive products to market.

It was therefore imperative to determine whether Merck and GSK's patents would prohibit HPV vaccine development in India. The two companies would have had to file patent applications and receive granted patents in India for them to have in that country the same intellectual property protection that they have in the developed world. There are several arguments about whether the companies may choose to seek patent protection in developing countries or not. On the one hand, it can be argued that because of limited recombinant vaccine production capacity in most LMCs, seeking patents in those jurisdictions is largely unnecessary. On the other hand, it may be argued that because middle-income countries in emerging

economies are potentially large markets for such vaccines, companies may choose to capitalize on them and may actively seek patent protection in these jurisdictions for their products. The crux of this case study was therefore to (1) determine whether universities and Merck and GSK had filed patent applications in India, and which, if any, were granted there, and (2) identify whether the claims of these patents prohibit Indian companies from developing alternate vaccine candidates.

As of December 2008, 18 of the 86 international applications were filed in India (Appendix 2). The universities and NIH have not sought patent protection for technologies underlying L1-VLP vaccines in India. Merck and GSK, however, have applied for patents on HPV vaccine compositions. GSK alone has filed 13 of these applications. The Indian Patent Office (IPO) has awarded 6 patents, 4 to GSK and 1 each to Wyeth Holdings Corp. and the University of Cape Town (South Africa). While determination of patent scope is complicated and sometimes the subject of costly litigation, the following is an analysis of patent claims based on my knowledge of these technologies.

Patent 203333 awarded to GSK claims compositions of a prophylactic vaccine that contains VLPs composed of L1 antigens from HPV 16, 18, 31, *and* 45. It appears that only a “biosimilar” vaccine containing L1-VLPs from all four HPV strains would directly infringe this patent. Therefore, an Indian manufacturer may be free to develop a bivalent HPV vaccine containing L1-VLPs for HPV-16 and -18 only or a quadrivalent vaccine containing any combination of three, two, or one of these four strains in addition to other unclaimed oncogenic strains. Patent 209780, also awarded to GSK, claims a vaccine composition comprising L1-VLPs for HPV-16, HPV-18 and an adjuvant containing aluminum hydroxide and 3-0-desacyl-4'-monophosphoryl lipid A (3dMPL). However, my analysis suggests that a bivalent (HPV-16, -18

L1-VLP) prophylactic vaccine developed by an Indian manufacturer would not infringe this patent if formulated with a different adjuvant. Additional patents awarded to GSK (Appendix 2) claim nucleotide sequences of HPV early antigens (214047) and compositions of combination vaccines containing HPV L1 antigens (202425) and other antigens respectively. These too are unlikely to constrain Indian vaccine manufacturers developing *Gardasil* or *Cervarix* “biosimilars.” The University of Cape Town patent claims methods to produce HPV-16 L1-VLPs in tobacco plants and their use in a vaccine composition. However, to date plant-based expression has been unsuccessful in yielding high amounts of purified HPV-16 VLPs,¹¹ thus limiting the commercial viability of this technology. Patent 220842 awarded to Wyeth covers polypeptides of HPV early antigens E6 and E7, which are likely to be used in therapeutic cervical cancer vaccine compositions but are less relevant to L1-VLP-based prophylactic vaccines. Merck’s 4 pending patent applications, claiming L1 nucleic acid sequences of HPV subtypes 31, 45, 52, and 58, optimized for expression in several yeast strains, are most relevant to this study. However, the Indian Patent Office may significantly narrow the scope of or deny some claims during examination. It is therefore difficult to assess whether Merck’s applications will affect vaccine development in India.

This analysis suggests that there may be much more freedom to produce first generation HPV vaccines in India than previously thought. However, currently marketed first-generation vaccines are costly to produce, even without patents guarding the technology. Furthermore, as few Indian companies have managed produce high enough yields of VLPs, successful production in India will require transfer of know-how from developed world institutions. Consequently, while uncertainty regarding freedom to operate may no longer be an obstacle, production barriers may prevent marketing of regionally manufactured first generation vaccines in the near future.

Developed country research institutions, aware of the inherent limitations of the current vaccine (it only protects against 70% of cervical cancer causing HPV strains and is known to miss several strains that are prevalent in LMCs) and other implementation challenges (requirement of three-dose regimen and cold chain storage), have expanded their efforts into novel second generation vaccine candidates that may be better suited for developing world use. Researchers at the NCI (John Schiller, Douglas Lowy, Richard Roden and colleagues) and Johns Hopkins University (JHU) have developed an L2 (minor capsid antigen)-based vaccine. This approach would protect against infection by all oncogenic strains and would eliminate the costs of increasing valency, that is, adding more L1 antigens from different HPV strains, to current vaccines.⁶³ They have jointly conducted this second-generation research with DCVMs, thereby recognizing the importance of their developing country research counterparts.

Indeed, NCI and JHU have partnered with Shantha Biotechnics (Shantha) to commercialize A L2 vaccine candidate. They jointly filed Indian patent application 6219/DELNP/2007 (Appendix 2) with the explicit rationale of preserving freedom to operate and market exclusivity for Indian partners.⁶⁴ Shantha has signed a Cooperative Research and Development Agreement (CRADA) with the NIH, gaining access to biological materials like codon-optimized plasmids, know-how and personnel training necessary for developing this vaccine. Shantha has also non-exclusively licensed this technology from JHU. Using an *E.coli* expression system to purify L2 antigenic peptides, Shantha hopes to lower development costs, thereby enabling significant vaccine price reduction.^{65, 66}

⁶³ Schiller et al. 2006. Vaccine.

⁶⁴ Personal Interview with Dr. John T. Schiller. 2007.

⁶⁵ Jagu et al. 2009. JNCI.

⁶⁶ Personal Interview With Shantha Biotech. 2007.

Indian patent application 131/CHENP/2007 also bears on second-generation vaccine development and is based on research performed at the University of Lausanne (Lausanne), Switzerland. Dr. Denise Nardelli-Haefliger and colleagues demonstrated that recombinant clones of attenuated *Salmonella* strains expressing HPV-16 and -18 L1 antigens can induce a strong immune response.^{67, 68} This technology would enable oral or mucosal immunization against HPV-16 and -18 infection. Lower development and implementation costs associated with this oral vaccine make it highly suitable for LMC use. To maximize the potential benefits of this technology to LMCs, Nardelli-Haefliger et al. assigned ownership of enabling IP to Indian Immunologicals Ltd (ILL).⁶⁹ ILL has a memorandum of understanding with Lausanne and has received biological materials, know-how, and training. ILL has also filed international patent applications (Appendix 3) but will not seek patent protection in OECD markets.⁷⁰ With assured access to essential patents and know-how, ILL has strong incentives to invest in oral HPV vaccine development. Both vaccines are currently in preclinical phase. Shantha projects a 2015 market entry at an initial price of \$15/dose.⁷¹ Both manufacturers believe, however, that prices will drop further as vaccine adoption increases, eventually reaching the \$1-2/dose price range, making broad access feasible.^{72, 73}

Serum Institute of India (Serum) and Bharat Biotech (Bharat) are both also developing L1 VLP-based vaccines.^{74,75} Serum's candidate will likely be a bivalent HPV-16 and -18

⁶⁷ Schiller et al. 2006. Vaccine.

⁶⁸ Fraillery et al. 2007. Clinical and Vaccine Immunology.

⁶⁹ Personal Interview with Denise Nardelli-Haefliger. 2007.

⁷⁰ Personal Interview with Indian Immunologicals. 2007.

⁷¹ Sinha. 2007.

⁷² Personal Interview with Shantha Biotech. 2007.

⁷³ Personal Interview with Indian Immunologicals. 2007.

⁷⁴ Personal Interview with Dr. Sanjay Singh. 2009.

⁷⁵ Personal Interview with Dr. Sumati Kandaswamy. 2009.

vaccine. The company will seek a non-exclusive license from the NIH for cell lines optimized for high expression of L1 antigens and will non-exclusively license the *Hansenula polymorpha* expression platform from Rhein Biotech (Germany). Serum anticipates a market entry of three to four years after project initiation.⁷⁶

In addition to the L1-VLP vaccine candidate, Bharat scientists are exploring a chimeric L2-HPV vaccine. They plan to express an L2-Hepatitis B small surface antigen (SAg) fusion protein in *Picchea pastoris* to produce VLPs containing HPV-L2 antigens at high density. Because the Hepatitis B surface antigen spontaneously assembles into VLPs, Bharat hopes to enable vaccine price reduction by circumventing high costs of purifying and assembling VLPs. Bharat filed a provisional patent application for this vaccine in India last year. Despite developing this technology in-house, Bharat may seek a non-exclusive license from the NIH for the cell lines used in neutralizing assays that measure immunogenicity of their vaccine candidates.⁷⁷

As these efforts are largely in the preclinical phase, they may still entail at least several years of development and testing before they can be marketed as direct competitors to *Gardasil* and *Cervarix*. Further compounding the problem is the fact that those developing follow-on HPV vaccines may have to get licenses from the institutions owning the patents to be permitted to market their product. This is a problem for HPV vaccines in particular because the university licensing terms are generally not publicly available, except when parties choose to disclose them voluntarily. It is therefore unclear which technologies are available for licensing. This uncertainty could pose a barrier to the implementation of second-generation vaccines with the capacity to have a dramatic impact on global health.

⁷⁶ Personal Interview with Dr. Sanjay Singh. 2009.

⁷⁷ Personal Interview with Dr. Sumati Kandaswamy. 2009.

4.2 ROTAVIRUS VACCINES: FROM DEVELOPMENT TO LICENSING

Rotavirus is an infectious pathogen that infects nearly all children under the age of five globally. An infection that causes vomiting, fever, and diarrhea, it often results in dehydration, which can lead to death if not treated immediately. Each year, over 500,000 children die from the disease, and over 2 million are hospitalized because of dehydration. The developing world bears a disproportionate number of Rotavirus-related deaths. 90% of deaths occur in low-income countries, with a 1 in 250 chance of dying from the infection in those regions in part due to poor facilities to enable immediate rehydration. In contrast, the risk of death in the United States is 1,000 times lower, at 1 in 200,000.⁷⁸ In India, diarrhea resulting from rotavirus is a leading cause of death for children under the age of five.⁷⁹ Each year, more than 100,000 children in that country alone die from Rotavirus-induced diarrhea.⁸⁰ Efforts to reduce the number of cases of diarrhea through home-based oral rehydration programs and provision of cleaner water have failed, largely because increased sanitation and clean water do not decrease the disease's prevalence and vomiting prevents the success of oral rehydration. While diarrhea-induced deaths are largely preventable, those in resource poor settings require access to immediate medical care (hydration with water, oral rehydration salts, and/or IV therapy) to overcome the disease.⁸¹ Few, however, can afford to do so. The Rotavirus vaccine therefore presents an opportunity to markedly reduce the number of deaths each year by preventing infection from the disease altogether.

4.2.1. The development of Rotavirus vaccines

4.2.1.a Development of Rotashield

⁷⁸ Rheingans. 2006.

⁷⁹ Saravanan et al. 2004. IJMM.

⁸⁰ Jain et al. 2001. J. Clin. Microbiol.

⁸¹ Rotavirus | Sabin Vaccine Institute. 2009.

Dr. Albert Kapikian and colleagues of the National Institute of Allergy and Infectious Diseases (NIAID) originally developed the first rotavirus vaccine – RotaShield. The vaccine was developed further through collaborations with Wyeth Pharmaceuticals⁸² and was first licensed for use in the US in August 1998.⁸³ However, it was voluntarily removed from the market after just one year because it was statistically shown to result in intussusception,⁸⁴ an unforeseen, adverse side effect in which a segment of the small intestines slides into another section of the intestines. This action blocks the passage of fluids and food and also cuts off the blood supply to the affected portion of the intestines.⁸⁵ Though it is treatable and is not immediately life threatening, surgery may be required if it cannot be corrected through normal means (barium or water-soluble contrast enema).⁸⁶ In developing countries where access to hospitals is not guaranteed, intussusception can likely lead to death within two to five days.⁸⁷

4.2.1.b. The first bovine reassortant rotavirus vaccine

Following the withdrawal of RotaShield from the market, interest in Kapikian’s human-bovine reassortant rotavirus vaccine (that was originally intended to be a second-generation candidate) grew. This quadrivalent vaccine, also developed in cooperation with Wyeth, is comprised of the G1, G2, G3, and G4 Rotavirus strains⁸⁸ that collectively account for almost 90% of circulating Rotavirus strains globally.⁸⁹ The vaccine can also be altered in formulation to become a hexavalent vaccine that includes the G8 and G9 strains that are predominantly found in

⁸² Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

⁸³ Dennehy. 2008. Clinical Microbiology Reviews.

⁸⁴ Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

⁸⁵ Intussusception - MayoClinic.com. 2009.

⁸⁶ Del-Pozo et al. 1999. RadioGraphics.

⁸⁷ Ng'walali et al. 2003. Legal Medicine.

⁸⁸ Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

⁸⁹ Griffin et al. 2000. J. Clin. Microbiol.

Africa and Latin America respectively.⁹⁰ Dr. Kapikian and Dr. Harry Greenberg (formerly of the NIH but now at Stanford University) have publications dating back to 1981 in the *Proceedings of the National Academies of Science* that indicate a specific process for making these vaccines (which involves combining a large quantity of genes from animal bovine Rotaviruses that are then attenuated in humans to induce an immune response.)⁹¹ The vaccine is protected by patents and pending applications in multiple international jurisdictions, including the United States, Europe, Canada, Japan, China, India, Korea, Brazil, and Australia.⁹²

Because of the interest companies from around the world showed in this technology, the NIH licensed it to eight institutions in 2005 (one in the United States and seven in the developing world): Aridis Pharmaceuticals (USA); Fundação Butantan (part of the Brazilian government); Bharat Biotech International, Biological E, Shantha Biotechnics, Ltd., and Serum Institute of India (all from India); and Chengdu Institute of Biological Products and Wuhan Institute of Biological Products (both based in China). The licensing terms include geographic fields of restriction, thereby preventing the companies from selling their vaccines globally and infringing on the profits of other institutions – Butantan was granted an exclusive license and is permitted to sell its vaccine throughout Brazil and Latin America, the Chinese companies can sell their products to China’s expanded program of immunization, while the four Indian companies were given rights to sell their vaccines within India and other developing countries excluding China, Brazil, and Latin America. Aridis Pharmaceuticals received an exclusive license to the technology and was granted the right to sell its vaccine in the United States, Europe, and Canada. The licenses include rights to the intellectual property as well as to biological materials

⁹⁰ Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

⁹¹ Greenberg et al. 1981. Proc. Natl. Acad. Sci.

⁹² Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

(including vaccine strains and the analytical reagents necessary for successful development). In licensing the technology in this way, the NIH Office of Technology Transfer and the U.S. Public Health Service sought to ensure that the vaccine could be successfully distributed on a global scale.⁹³

4.2.1.c Development of Rotateq

Merck, which developed Rotateq, a bovine reassortant Rotavirus vaccine similar to that of the NIH (differing only in the specific bovine virus used), licensed its technology from Dr. Fred Clark and Dr. Paul Offit of the Children's Hospital of Philadelphia and the Wistar Institute in 1991. The polyvalent vaccine comprises the G1, G2, G3, G4, and P1 rotavirus antigens that collectively prevent against 80% of known gastroenteritis-causing strains. It has been largely successful to date, with a 70% efficacy rate against rotavirus gastroenteritis and a 100% prevention rate against severe rotavirus-related gastroenteritis following the first round of vaccination in Phase II clinical trials.⁹⁴

4.2.1.d Development of Rotarix

GSK-controlled IP for Rotarix, its Rotavirus vaccine, will likely also inhibit Rotavirus vaccine development in the United States and other OECD countries. Initially developed by Cincinnati Children's Hospital, which patented its technology in 1995 (US5474773), the vaccine is made from a live, attenuated human rotavirus strain (89-12) and comprises the G1 antigen, which is the most prevalent strain worldwide.⁹⁵ The technology was sub-licensed to Avant Immunotherapeutics in 1995⁹⁶ for further development into a marketable product.⁹⁷ Then, in

⁹³ Rotavirus Vaccine: NIH Office of Technology Transfer. 2009.

⁹⁴ Wuethrich. 2004.

⁹⁵ Wuethrich. 2004.

⁹⁶ USA. 2005. Securities and Exchange Commission.

⁹⁷ Dennehy. 2009. Clinical Microbiology Reviews.

1997, GSK sublicensed the technology from Avant⁹⁸ and further modified it through cloning and tissue culture passaging of the original strain. The vaccine has proven to be generally effective in clinical trials, demonstrating a 73% efficacy rate against Rotavirus-induced gastroenteritis and a 90% rate against severe Rotavirus-induced gastroenteritis. In addition, it has also been shown to provide cross-protection for severe Rotavirus-induced gastroenteritis resulting from other serotypes. Indeed, the vaccine has an 83% efficacy rate against illness caused by the G9 strain that is common in Brazil. Further improving its utility is the fact that it can be administered simultaneously with other childhood vaccines without adversely affecting the level of immune response.⁹⁹

4.2.2. The role of patents in the availability of rotavirus vaccines globally

Patents make it difficult for any company in the United States and other OECD countries to fully realize the goal of global Rotavirus vaccine distribution. In the United States especially, vaccine prices will likely remain high because the patent monopoly that Merck and GSK have over their respective vaccine technologies makes it largely impossible for other companies in the developed world to enter the market with similar products.

Merck has received an additional five patents that cover the bovine reassortant Rotavirus vaccine technology as a whole (several reassortant viruses *and* methods for producing them) rather than the specific bovine strain used to develop Rotateq. According to Dr. Harry Greenberg, formerly of the NIH and now at Stanford University, Merck should not have received these patents at all due to prior art.¹⁰⁰ Indeed, as mentioned previously, he and Dr. Kapikian collaborated to develop the technology in the 1980s (which they published in the PNAS in 1981

⁹⁸ Rotarix Oral Vaccine for Rotavirus Gastroenteritis. 2008. P&T.

⁹⁹ Wuethrich. 2004.

¹⁰⁰ Prior art refers to information that was in the public domain prior to a date that might be relevant to a given patent application's claim of originality.

and patented on February 18, 1986 – US4571385). However, the USPTO inexplicably granted Merck five patents (Appendix 4) that still stand; interference proceedings to challenge them have not been initiated to date. Consequently, these patents may discourage any company from producing a bovine reassortant Rotavirus vaccine the United States and other OECD countries. Therefore, while Aridis Pharmaceuticals has exclusive rights to the bovine reassortant technology developed by the NIH, Merck’s granted patents appear to limit it from selling such a product in the United States.¹⁰¹ As a result, Aridis is primarily using this license to develop a method of storing Rotavirus vaccines at room temperature. While such an innovation would be of great value to vaccine manufacturers globally, Aridis is unlikely to bring a direct competitor to Merck’s reassortant vaccine to market.¹⁰²

Similarly, GSK’s control over IP relating to the human Rotavirus candidate vaccine prevents the entry of other competitors in the developed world. As a result, high prices for this particular Rotavirus vaccine remain a reality globally, as much of vaccine development occurs in the developed world. The private market price for Rotateq currently stands at \$69.59 per dose, pricing the full three doses at \$208.77. Though the Center for Disease Control and Prevention (CDC) has negotiated a lower price per dose – \$57.20 – for those with demonstrated need, the vaccine is still largely unaffordable.¹⁰³ Rotarix is also still too expensive, costing \$101.75 per dose, resulting in a \$203.50 price tag for the two-dose regimen.¹⁰⁴ Furthermore, the CDC-negotiated price of \$83.25 per dose¹⁰⁵ is also much too high for those in the developing world who stand to benefit the most. It is clear that an alternate Rotavirus vaccine development

¹⁰¹ Personal Interview With Dr. Harry Greenberg. 2009.

¹⁰² Interview with Dr. Albert Kapikian and Dr. Mukul Ranjan. 2009.

¹⁰³ Vaccines: VFC/CDC Vaccine Price List. 2009.

¹⁰⁴ Weycker et al. Vaccine. 2009.

¹⁰⁵ Vaccines: VFC/CDC Vaccine Price List. 2009.

mechanism will be necessary to make these vaccines more affordable. While Merck and GSK both hope to sell the vaccine for \$5-8 in low-income countries,¹⁰⁶ it will still likely be unaffordable for those who live on dollars a day at best. Prices therefore need to drop further.

GAVI has subsidized Rotavirus vaccines for some developing countries in Latin America, but introduction in Asian and African countries is expected to begin only in 2010.¹⁰⁷ Furthermore, it is likely that some middle-income countries will remain ineligible for GAVI subsidies. It is therefore imperative to increase availability of low-cost vaccines from alternate suppliers to achieve global coverage.

4.2.3. Does IP prevent developing country vaccine manufacturers (DCVMs) from developing “generic” rotavirus vaccines?

As demonstrated in the HPV vaccine case, DCVMs have a proven capacity to develop high quality, low-cost vaccines that developing country national immunization programs and organizations like UNICEF and GAVI can effectively procure and subsidize. Regionally manufactured Rotavirus vaccines may therefore be more viable alternatives to those developed by Merck and GSK. Given NIH’s efforts to non-exclusively license its bovine reassortant technology to six developing world vaccine companies, the goal of this case study was to understand whether IP is preventing Indian companies from taking advantage of this open access to technology and developing a direct competitor to Merck’s vaccine.

Patents will not impede DCVM development of either a direct Merck competitor or any other candidate. To date, 30 US patents have been granted, corresponding to 23 PCT applications. 13 entities own these patents: non-profits own 21 of these granted patents and for-profits own 9. The US Department of Health and Human Services (US DHHS) jointly owns 3

¹⁰⁶ Personal Interview With Dr. Harry Greenberg. 2009.

¹⁰⁷ Eligible Nations Voice Support. Rotavirus Update. 2007.

granted patents with Dyncorp and 1 with the CDC. Overall, the US DHHS individually owns the most with 12 granted patents followed by Merck with 5, GSK with 3 and Wyeth with 2 (Appendix 4). Of these, only GSK has filed patents applications in India, with 2 pending: 670/KOLNP/2008 and 3258/KOLNP/2007. The former claims a method of inducing an immune response against a non-GxPy Rotavirus strain using an attenuated Rotavirus strain of the GxPy type. The vaccine's composition comprises proteins encoding VP4 and VP7 gene sequences and specific variants of those sequences. The latter application claims a liquid Rotavirus immunogenic composition suitable for oral administration to a human infant comprising a live attenuated (HRV P43 or HRV 89-12C2) strain or a Rotavirus antigen, a sugar (dextrose or sucrose) and a carboxylate with a formulation having a pH of between about pH 5.0 and about pH 8.0. Neither patent protects the bovine reassortant technology that the NIH licensed to Bharat Biotech (Bharat), Shantha Biotech (Shantha), Biological E, and Serum Institute of India (Serum). In addition, both patents can be worked around, even if they are granted in their entirety, by using different strains or formulations. Therefore, it is unlikely that Indian companies will confront IP barriers that will impede their efforts to develop low-cost Rotavirus vaccines.

4.2.4. Ongoing Indian DCVM efforts to develop generic rotavirus vaccines

Shantha and Serum are, to the best of my knowledge, in the process of developing candidate vaccines based on the bovine reassortant technology they non-exclusively licensed from the NIH. It is not apparent that either company has identified an alternate method of production that can better enable dramatic price reductions. Rather, the prevailing opinion among the experts with whom I spoke is that the cost of production is much lower in India than in any developed country in North America or Western Europe. They therefore anticipate lower prices

for this reason alone.¹⁰⁸ However, it is difficult to determine with any certainty whether this will be the case. Sanofi Aventis, one of the four largest multinational vaccine-producing pharmaceutical companies, recently acquired Shantha, and as my visit coincided with the early days of the merger, Sanofi prevented scientists from speaking with me as planned. Circumstances also prevented me from speaking with the head of the Rotavirus vaccine project at Serum. Efforts to obtain this information following my return to the United States in August 2009 were unsuccessful. Indeed, scientists and technology transfer professionals at the NIH who developed and licensed the enabling technology were unwilling to share any information about either company's project. As a result, it is unclear to what extent either project has advanced, when either candidate will enter the market, and what the anticipated market entry price might be.

Bharat, however, is forging ahead in a novel Rotavirus vaccine project that originated through two independent research collaborations that later merged into one: the first partnership was between Dr. Durga Rao of the Indian Department of Biotechnology and Dr. Greenberg, while the second was a joint effort between Dr. Maharaj K. Bhan, formerly of the All India Institute of Medical Sciences, New Delhi and Dr. Roger Glass of the Fogarty Center at the NIH (formerly of the CDC). These collaborations were made possible through the Indo-US Vaccine Action Program (VAP) – created in 1987 when the United States and Indian governments signed a Memorandum of Understanding – that recognized the need for new vaccines that could capitalize on advances in biotechnology to target diseases prevalent in India.¹⁰⁹ Both Indian

¹⁰⁸ Interview with Dr. Albert Kapikian and Dr. Mukul Ranjan. 2009.

¹⁰⁹ Background, US-Indo Vaccine Action Program, DMID, NIAID, NIH.

scientists received funding through this program when they partnered with their American colleagues to collaborate on their Rotavirus vaccine research.¹¹⁰

Drs. Rao and Greenberg conducted initial research and development on the 321 Rotavirus strain. Drs. Bhan and Glass worked on the 116 strain, a naturally occurring Rotavirus strain containing ten human genes and one bovine gene (serotype G9). The 116 strain, which was identified in neonatal nurseries in India, proved to be more infectious and immunogenic than did the 321 strain. While Dr. Glass and the CDC patented the 116 strain in the United States (US5773009), my analysis suggests that they did not file in India. As part of the collaboration, Bharat obtained both strains in a license-free agreement before deciding, in conjunction with the four researchers, to pursue the 116 strain for development of an attenuated, oral vaccine. The company has received significant funding from the Bill and Melinda Gates Foundation and PATH to develop its vaccine, which appears to be more immunogenic than any of the other vaccines currently on the market. Phase 3 clinical trials funded by the Gates Foundation and facilitated by PATH are expected to start this year in India. Bharat anticipates an initial market price of approximately \$2 per dose, but has full confidence that with widespread vaccine adoption, it can further lower the price to \$1 per dose or less.¹¹¹

4.3 HEPATITIS B VACCINES: FROM DEVELOPMENT TO LICENSING

The Hepatitis B virus, which causes a potentially life threatening liver infection, is 50 to 100 times more infectious than is HIV. Transmitted in much the same way as HIV – through direct contact with infected blood or other body fluids – the virus differs from HIV in that it can survive outside the body for a minimum of seven days and remains as infectious during this time period as it is when within the body. Consequently, 2 billion people worldwide have contracted

¹¹⁰ Personal Interview with Dr. Harry Greenberg

¹¹¹ Personal Interview With Dr. Harry Greenberg. 2009.

the disease, and 350 million are battling chronic liver infection. Common avenues for transmission are: (1) from mother to infant at birth, (2) early childhood infections when a child comes in contact with an infected family member, (3) unhygienic needle sharing, (4) blood transfusions, and (5) sexual intercourse. Approximately 600,000 people die annually from chronic Hepatitis B infection, with 25% of adults who were infected with Hepatitis B as children dying from liver cancer or cirrhosis (scarring of the liver). Age of infection is a critical determinant for whether an infected patient develops a chronic infection. Indeed, those who contract the virus as young children are much more likely to face chronic infection. 90% of infants infected in their first year of life will develop chronic infections, while 30-50% of children between the age of one and four who contract the virus will become chronically infected. In contrast, 90% of those infected as adults can overcome the disease and return to complete health in six months.¹¹²

Like HPV and Rotavirus, Hepatitis B is most common in the developing world, especially in Asia and the Indian sub-continent. 8-10% of adults in China and other Asian countries are chronically infected with Hepatitis B. Furthermore, Hepatitis B-induced liver cancer is one of the most common causes of death from cancer in Asian men and plays a large role in cancer development in women. On the Indian sub-continent, 2-5% of the population as a whole is chronically infected with Hepatitis B. This is in stark contrast to Western Europe and North America, where less than 1% of the entire population has chronic Hepatitis B infection. There is, unfortunately, no perfect treatment for the disease. The goal of most health care professionals is to keep patients comfortable and to ensure adequate nutrition. Efforts are made to keep patients hydrated, especially as they experience vomiting and diarrhea. While interferon

¹¹² WHO | Hepatitis B. 2009.

and anti-viral agents can be used to treat chronic Hepatitis B infections, these treatments can cost upwards of several thousand dollars and are consequently inaccessible to patients in the developing world.¹¹³ Therefore, as is the case with both HPV and Rotavirus infections, there is a real need for widespread access to Hepatitis B vaccines in the developing world to prevent Hepatitis B infections.

4.3.1 Hepatitis B vaccine development history

Hepatitis B vaccine development first became a possibility in 1965 when Dr. Baruch Blumberg and colleagues at the Fox Chase Cancer Center (FCCC) isolated whole Hepatitis B viruses from blood. Further research conducted by Saul Krugman at New York University demonstrated that injecting blood from patients with Hepatitis B that had been heated to kill the viruses themselves induced some immune response in healthy individuals. Based on this discovery, Blumberg and Irving Millman hypothesized a method of vaccine development using Hepatitis B surface antigens isolated from the blood of carriers of the virus. The FCCC filed a patent for this method in 1969,¹¹⁴ which was granted in 1972 (US3636191).¹¹⁵ Maurice Hilleman and colleagues at Merck, who had to this point been independently conducting similar research, licensed the vaccine technology from the FCCC in 1971 and, after years of research and testing, developed a plasma-derived vaccine – Heptavax¹¹⁶ – that underwent clinical trials in 1980,¹¹⁷

¹¹³ WHO | Hepatitis B. 2009.

¹¹⁴ Patlak. 2009.

¹¹⁵ Blumberg. 1972.

¹¹⁶ Vaccine History. 2009.

¹¹⁷ Patlak. 2009.

was licensed for use in the United States in 1981,¹¹⁸ and was first marketed in 1982.¹¹⁹ The vaccine was shown to be 90% effective against Hepatitis B with no adverse side effects.¹²⁰

Dr. William Rutter of the University of California – San Francisco began the effort to develop a recombinant Hepatitis B vaccine in 1977 when it became apparent that large-scale production of Merck’s plasma-derived vaccine would be difficult. Indeed, obtaining enough blood from those carrying the virus that was not contaminated with other viruses was a challenge. There was concern that Merck would not be able to meet the market demand. A recombinant vaccine could ensure a limitless supply to the biological materials necessary to develop the vaccine while simultaneously guaranteeing that the samples would remain free of other viruses. Rutter, however, struggled to find an expression system that would allow for recombinant production of the Hepatitis B surface antigen (HBsAg). His experiments using bacteria to produce the particles were unsuccessful. His collaborative partnership with Benjamin Hall and colleagues of the University of Washington, however, yielded the necessary breakthrough. The two were successfully able to produce the recombinant antigen using a yeast-based expression system. They ultimately formed the Chiron Corporation both to develop a recombinant Hepatitis B vaccine in conjunction with Hilleman and colleagues at Merck and to use their expertise in recombinant technology to produce other drugs and vaccines. Following nine years of research and development, the FDA licensed Merck’s recombinant vaccine for widespread use in 1986.¹²¹ This technology has since completely replaced the original plasma-

¹¹⁸ Vaccine History. 2009.

¹¹⁹ Goldstein et al. 2002. Journal of Infectious Diseases.

¹²⁰ Patlak. 2009.

¹²¹ Patlak. 2009.

derived vaccine, which was discontinued in 1990 and is no longer marketed in the United States.¹²²

However, as with the HPV and Rotavirus vaccines currently, Hepatitis B vaccines were much too expensive for most sectors of the developing world population to afford. It was the most expensive vaccine of its time, costing anywhere from \$50-80 per dose for the three dose regimen.¹²³ Consequently, a cheaper vaccine was necessary. This need provided an opportunity for Indian manufacturers to break out of their role as predominantly manufacturers of generic drugs. All relevant patents expired well before the Indian companies undertook their respective projects. As a result, licenses for the technology they hoped to use were unnecessary and access to biological materials and know how was unlimited.

4.3.2. DCVM Hepatitis B Vaccine Development Efforts

4.3.2.a. Shantha Biotech (Shantha)

Shantha Biotech, the first Indian pharmaceutical company to begin developing a generic Hepatitis B vaccine in 1992, engaged in this project when participants in a World Health Organization (WHO) meeting indicated their belief that DCVMs were incapable of manufacturing a recombinant vaccine. At that time, only the United States and Cuba had a proven capacity to do so successfully. With few viable competitor vaccines available to help drive down prices (only one from GSK was also available in the market), Merck's imported vaccine was much too expensive, costing approximately \$13 per dose in India. Furthermore, with no government plans in place to include the vaccine in its national immunization program for children (which subsidizes the purchase and administration of childhood vaccines), there was a demonstrated need for a low-cost alternative. Dr. Varaprasad Reddy, founder and CEO of

¹²² Vaccine History. 2009.

¹²³ GAVI Alliance Report.

Shantha, saw an opportunity to meet this need while simultaneously putting India's vaccine development capacity on the world's radar. The company tried to license recombinant Hepatitis B vaccine technology from Genentech in 1992. That agreement, however, never took root.¹²⁴

Shantha ultimately developed its vaccine – which comprises the Hepatitis B surface antigen – independently, only non-exclusively licensing its yeast-based expression system (*Picchea pastoris*) from RCT Technologies in San Diego, California. This effort differs from the Rotavirus and HPV vaccine cases in two respects: (1) scientists at Shantha did not go abroad for additional training. They instead obtained any additional know how necessary for development from scientific literature and expertise available at the Center for Cell and Molecular Biology (a premiere national laboratory). (2) The intellectual property landscape at the time was of little concern. Indeed, the presence of Merck and GSK's product patents in several jurisdictions around the world in 1992 did not impede Shantha's research and development efforts.¹²⁵ Prior to 1995, the Indian Patent Office did not grant product patents in any form.¹²⁶ Shantha and all other regional manufacturers in the country were therefore free to develop Hepatitis B vaccines that were contemporaries of Merck and GSK's products. Furthermore, while several process patents did exist, Shantha was able to work around them by being the first to use the yeast-based expression system to develop its generic vaccine candidate. When Shantha brought its vaccine to market in 1997 under the name of Shanvac B, all relevant patents had expired (Pfizer also marketed the vaccine as HepaShield for some time).¹²⁷ Consequently, there was no chance that the vaccine could infringe existing patents. In the years since, given the novelty of Shantha's yeast-based expression system of approach, the company has made its mark on the Hepatitis B

¹²⁴ Personal Interview with Dr. Varaprasad Reddy. 2007.

¹²⁵ Personal Interview With Shantha Biotech. 2007.

¹²⁶ Milstein et al. 2007. Vaccine.

¹²⁷ Personal Interview With Shantha Biotech. 2007.

vaccine landscape, filing for patents in India. To date, they own two process patents (patent numbers are unavailable) there and also have one pending application.¹²⁸

Shantha's entry into the Hepatitis B vaccine market facilitated an unparalleled level of market competition. 7 Indian companies (Bharat Biotech, Bhat Bio-Tech India, Biological E, Indian Immunologicals, Panacea Biotech, Serum Institute of India, and Wockhardt) all developed different versions of the recombinant Hepatitis B vaccine in the following years,¹²⁹ resulting in a dramatic price reduction. Now, Shantha's vaccine sells for approximately 4-5 rupees (\$0.10) per dose.¹³⁰ Both Bharat and ILL's respective vaccines are discussed in greater detail here because they directly followed Shantha's candidate.

4.3.2.b Bharat Biotech (Bharat)

Bharat began research and development of a Hepatitis B vaccine candidate of its own – Revac B – in 1996, shortly after Shantha, developing the world's first cesium chloride-free Hepatitis B vaccine (meaning a vaccine that does not need preservatives).¹³¹ This company, which launched the vaccine in October 1998, recently exceeded 150 million doses that were developed and distributed.¹³² However, conversations with Bharat did not yield specific information about additional reasons for engaging in Hepatitis B vaccine development aside from the widespread need for more affordable alternatives nor about the specific technology and/or partnerships they used to bring this product, their first vaccine, to market.

4.3.2.c. Indian Immunologicals (ILL)

¹²⁸ Intellectual Property Policy: Patents.

¹²⁹ Frew et al. 2007. Nature Biotech.

¹³⁰ Personal Interview With Dr. Varaprasad Reddy.

¹³¹ Revac-B World's First Cesium Chloride Free Recombinant Hepatitis-B Vaccine.. 2009.

¹³² Bharat Biotech's REVAC-B+TM - Hepatitis B Vaccine Crosses 150 Million Mark. 2008.

ILL began developing its Hepatitis B vaccine in 2001 following the entry of Shantha and Bharat's candidates to the market. Its impetus to enter the field was slightly different from its earlier counterparts, however, in that it was based on a calculated business strategy. Despite the fact that two indigenously developed vaccines were already competing with Merck and GSK's vaccines in India, ILL's business professionals indicated that the market could accommodate the entry of another similar product. Indeed, a third Hepatitis B vaccine could achieve even further price reductions, thus allowing ILL to realize their institutional goal of offering low-cost vaccines. Their vaccine – Elovac-B – was developed in collaboration with the India Institute of Science in Bangalore, India, which developed the enabling technology that the company ultimately used. ILL was responsible for conducting the preclinical research and development in addition to conducting the necessary clinical trials for regulatory approval. The company, like Shantha and presumably Bharat, faced no IP barriers, as the strain that the India Institute of Science used was different from that of Merck, GSK, Shantha, and Bharat. This slight variation ensured that ILL's vaccine would not infringe existing process patents (again, product patents were not granted in India at this time so they were a nonissue with respect to generic vaccine development).

What distinguishes ILL's vaccine from that of its indigenously developed vaccine counterparts, however, is that its method of distribution has been much more attuned to India's limited infrastructural capacity. Since its inception as a company that almost exclusively developed vaccines for agricultural purposes, ILL has partnered with the Abhay Clinics – a series of clinics and centers scattered across the country in largely rural settings – to increase its capacity to reach low-income patients who stand to benefit the most from vaccination. This collaboration has enabled the company to vaccinate millions of children directly since its

introduction in 2006, thereby largely eliminating the need for assistance from philanthropic organizations like UNICEF, PATH, and GAVI, among others.¹³³

V. DISCUSSION OF FINDINGS AND RECOMMENDATIONS

Ultimately, granted patents, and by extension, licenses, do not appear to present a barrier to regional HPV vaccine manufacturing in India. It seems likely that regional manufacturers can work around both companies' respective intellectual property portfolios in India, using alternate methods of development that can still enable vaccine production. As the Hepatitis B and Rotavirus vaccine case studies demonstrate, developing countries have the capacity to engage in complex research and development efforts to develop efficacious vaccines. These candidates are in several instances much better suited for LMC use. In addition, their dramatically lower price tags make them more appropriate candidates for widespread implementation in resource-poor regions. However, the three case studies demonstrate that patent filings on enabling technologies in India are increasing with each successive vaccine development effort. Indeed, while there were no filings for the Hepatitis B vaccine in India and only 2 patents filed for the Rotavirus vaccine, there have been 18 filings for the HPV vaccine, the vaccine developed most recently. This trend suggests that India is becoming increasingly prominent as a potential market for vaccine sales. Consequently, there are several factors that are necessary to ensure that regional manufacturing remains a viable development pathway in the future: (1) improved IP transparency and capacity for freedom to operate analyses, (2) a proactive approach to IP management by universities and funders that supports regional manufacturing, and (3) increased use of collaborative research partnerships.

5.1. Improve IP Transparency and Capacity for Freedom to Operate Analyses

¹³³ Personal Interview With Indian Immunologicals. 2007.

Patent-related barriers, real or perceived, could significantly hinder developing country vaccine manufacturing (DCVM) efforts. It is, however, often difficult to determine whether DCVMs have freedom to operate because of uncertainties in finding patents and interpreting claims language and the fate of pending applications. Therefore, even if IP does not preclude vaccine development efforts, an inability to clearly identify and analyze such information presents a significant barrier in itself.

Recent studies suggest that the lack of IP transparency could be a major impediment for DCVMs exploring new vaccine candidates.¹³⁴ Lack of patent claim information in publicly available Indian patent databases made my own research slow and expensive. My experience mirrored those of Serum¹³⁵ and Bharat. Indeed, Bharat's R&D was delayed due to uncertainty about the status of patent protection for HPV antigens in India.¹³⁶ Moreover, many countries in Africa, Latin America and Southeast Asia – potential markets for HPV vaccines – lack online patent databases, making it very difficult to determine which LMCs have pending or granted patents. LMC companies generally lack the substantial financial and human resources necessary to perform freedom to operate (FTO) analyses using proprietary databases. Indeed, Shantha, ILL, and Bharat often rely on researchers to conduct in-house patent searches.^{137, 138, 139}

Creating resources to map and update the IP landscape for novel vaccines could facilitate regional manufacturing efforts. Organizations including the WHO and the World Intellectual Property Organization (WIPO) should create policies that support the training of developing countries in conducting FTO analyses and should even develop resources for patent landscaping.

¹³⁴ Milstein et al. 2007. Vaccine.

¹³⁵ Personal Interview With Yuvaraj Dalvi. 2009.

¹³⁶ Personal Interview With Dr. Sumati Kandaswamy. 2009.

¹³⁷ Personal Interview With Shantha Biotech. 2007.

¹³⁸ Personal Interview With Indian Immunologicals. 2007.

¹³⁹ Personal Interview With Dr. Sumati Kandaswamy. 2009.

For example, the WHO Initiative for Vaccine Research could formally coordinate such services to advise regional manufacturers on potential IP barriers for vaccine development. These efforts could be developed and managed in partnership with the Developing Country Vaccine Manufacturing Network.

In addition, universities can also help promote IP transparency. Secrecy surrounding licensing exacerbates uncertainties in FTO analyses. Publicly available licensing information can prevent regional manufacturers from wasting time and money on technologies that patents and licenses block. More importantly, illuminating unblocked pathways can create incentives to commercialize vaccines that are of little interest to OECD manufacturers. Universities owning upstream technologies can promote and compel disclosure of licensing terms as part of licensure to improve transparency. Alternatively, sponsors of university research can make transparency a condition of funding by stipulating (1) disclosure of what geographic regions and fields of use exclusive licenses cover or (2) publication of licensing contracts. Regardless of the method, universities and their sponsors should adopt policies that explicitly promote IP transparency as a vehicle to promote low-cost vaccine access.

Finally, governments of developing countries with burgeoning biotech industries should commit resources to create comprehensive, accessible electronic patent databases. Furthermore, they should both offer educational resources on IP management and provide follow-on training to their national patent offices to keep patent examiners up to date on technical advances. Doing so can help these officers to identify prior art and prevent egregious patenting of biopharmaceuticals in developing nations.

5.2. Proactive Approach to IP Management Strategies by Universities and Funders to Support Regional Manufacturing

Universities and non-profit research institutions exploring new HPV vaccine can expedite access to technology in LMCs. As primary generators and gatekeepers of IP for vaccine technologies, academic institution IP management practices will greatly affect regional vaccine manufacturing. The Lausanne-ILL partnership, for example, harnesses DCVM capacity to commercialize a vaccine candidate with a potentially high public health impact in LMCs despite little commercial interest in OECD countries. For example, regional manufacturers can easily identify technologies available for licensing and potential partners for vaccine development if a central portal or electronic clearinghouse of all HPV vaccine technologies is created. The NCI-JHU-Shantha partnership to commercialize L2-based vaccine technology further illustrates how IP management can create a pathway for product access in low-income markets. The same applies for the NIH's collaborations with both Shantha and Serum to develop Rotavirus vaccines.

University licensing terms are generally not publicly available, except when parties choose to disclose them voluntarily. This has precluded a definitive analysis of whether Rochester, Queensland, and Georgetown preserved freedom to sublicense HPV vaccine technologies or subsequent improvements to developing country vaccine manufacturers when negotiating exclusive licenses with Merck and MedImmune. If they did not, then the exclusive licenses that Queensland, Georgetown, and Rochester all awarded to Merck and GSK and the NCI's licenses that converted from non-exclusive to co-exclusive licenses may delay direct access to first generation vaccines or improvements on them for many more years.

The licensing of vaccine technologies underlying *Gardasil* and *Cervarix* does not conform to recent university technology transfer practice guidelines to maximize benefit for the global poor.^{140,141} This is understandable because the licenses in question were crafted in the

¹⁴⁰ Chokshi et al. 2007. JAMA

1980s before these guidelines were developed. Additionally, limited recombinant vaccine production capacity in LMCs rendered humanitarian licensing largely impractical at the time. The resulting inaccessibility of HPV vaccines, however, illustrates why recently recommended practice guidelines deserve attention, especially as new technologies for prophylactic or therapeutic vaccines emerge.

Moving forward, universities and other non-profit research institutions should adopt IP management strategies that preserve options for DCVMs. Preferred practices include default non-exclusive licensing, exclusive licenses with geographic fields of restriction (to ensure LMC companies have FTO), retaining rights to sublicense to regional manufacturers, non-profit organizations and/or public-private partnerships, humanitarian use clauses for patented technologies and products, and “White Knight” clauses to ensure vaccine affordability.^{142, 143} (White Knight clauses, developed by Dr. Maria Freire – formerly the director of the Office of Technology Transfer at the NIH – were based on the notion that there is more to be considered about the NIH’s business dealings than simply financial terms. Originating when she encouraged a small company called White Knight to donate their product to assist the CDC during the Ebola virus outbreak in the mid-1990s, the clause is an implicit agreement that those with exclusive licenses to technologies will do good for the community as an acknowledgement of taxpayers’ contributions to development efforts.)¹⁴⁴ In addition, while several universities in the United States have recently voluntarily adopted practice guidelines that promote access (as put forth in AUTM’s “9 Points” document), others have not. University administrators and their technology

¹⁴¹ Chaifetz et al. 2007. Globalization and Health.

¹⁴² Mahoney et al. 2004. Vaccine.

¹⁴³ Salicrup et al. 2006. Biotechnology Advances.

¹⁴⁴ Coulombe. 2000. The NIH Catalyst.

licensing officers should therefore articulate and adopt policies that indicate their commitment to promoting access to vaccines and other biomedical products in LMCs.

5.3. Increase use of collaborative research partnerships

In recent years, drugs and vaccines with specific benefits to the developing world have become increasingly available on the market. The HPV vaccine is just one of many such examples. There is, however, a growing trend in the inaccessibility of these vaccines in low-income regions due to their high cost. Developing country vaccine manufacturers (DCVMs) could help surmount many of these access barriers.

Researchers and DCVMs affirm that know-how, in addition to access to intellectual property, is also crucial for developing new vaccines.¹⁴⁵ Even when technologies are in the public domain or are available for licensing, vaccine development requires considerable expertise.¹⁴⁶ Universities and other non-profits can address this need by creating collaborative research partnerships modeled, for example, on the Indo-US Vaccine Access Project.^{147,148} Transfer of three second-generation HPV vaccine technologies to Indian companies potentially increases the likelihood of producing a vaccine better suited for LMCs than current vaccines. Oral, needle-free delivery of HPV vaccines, for example, might reduce the risk of infection of other sexually transmitted agents like HIV and HSV, eliminate multiple health care visits, and increase patient compliance in resource-poor regions if doses can be administered at home as reconstituted oral drops. Collaborative partnerships with DCVMs may also produce vaccines designed from the outset to meet specific implementation characteristics of resource-poor regions such as heat stable formulations, single-dose, or combination vaccines.

¹⁴⁵ Milstein et al. 2006. Health Affairs.

¹⁴⁶ Batson et al. 2008. Health Affairs.

¹⁴⁷ Rotavirus Vaccine: NIH Office of Technology Transfer.

¹⁴⁸ Salicrup. 2007. Nature Biotechnology.

The efforts of Bharat Biotech especially with respect to its Rotavirus vaccine project are a testament to the widespread, rapid innovation that occur when developed country institutions make a conscious effort to promote DCVM vaccine development. Indeed, Bharat only began developing its vaccine candidate in 2001.¹⁴⁹ That the company has managed to develop a novel vaccine for the first time in its country's history in just eight years is indicative of what collaborative research and development partnerships can accomplish.

Furthermore, advance market commitments (AMCs) – in which a government, international public health agency, or philanthropic organization commits to purchasing products that meet previously specified conditions – may also increase access as it provides incentives for R&D of essential medicines that target predominantly neglected diseases. In partnering with DCVMs using advanced market commitment agreements, organizations like the Bill and Melinda Gates Foundation and PATH can ensure development of vaccines that are not only inexpensive but that also take into consideration limitations in implementation infrastructures in addition to targeting neglected diseases. These agreements can complement existing vaccine access mechanisms, thereby using a multi-pronged approach to increase access to low-cost vaccines. Philanthropic agencies and other public-private partnerships that engage in AMCs should clearly articulate policies that preserve a sustainable pathway for low-cost vaccine availability. Indeed, they should ensure that technologies and IP are made accessible to DCVMs engaging in vaccine development.

6. Conclusions

With new vaccine candidates including those targeting Malaria and AIDS under development, it is likely that vaccines that can potentially have a large impact on global health

¹⁴⁹ Personal Interview With Dr. Harry Greenberg. 2009.

will enter the market in the next two decades. Organizations like UNICEF and GAVI will dedicate their resources to procuring them as soon as possible. Distribution of expensive, older vaccines targeting diseases like Rotavirus and HPV will therefore face stiff competition for the limited procurement funds available.¹⁵⁰ Consequently, the ongoing dialogue regarding vaccine affordability and accessibility in the developing world should focus more on DCVM capacity building as opposed to subsidization methods alone, which are unsustainable in the long-term. Indeed, funders like GAVI should commit to procuring the lowest cost vaccines available. Doing so will likely stimulate DCVM efforts.

IP management strategies that can better promote future DCVM efforts should be a critical component of these discussions as well. While IP-related barriers are not hindering current HPV and Rotavirus vaccine development project in India, this appears to be purely accidental. The practice of patenting in developing countries was not common in the late 1980s and early 1990s when these two vaccines were initially developed. Consequently, only a limited number of patents were filed in India, a fact that could possibly be true in other developing countries as well. The upward trend in patenting of vaccine-related technologies in India, however, indicates that India and other emerging economies are being increasingly viewed as potentially profitable markets. With DCVMs from China, Brazil, and Cuba, among others, entering the market with vaccines ranging from Hepatitis B to Japanese Encephalitis,¹⁵¹ there is a real need to ensure that patents will not stifle this growing manufacturing capacity for high quality, low-cost candidates.

Academic research institutions, from which most vaccine technologies emerge, can play an important role in supporting regional manufacturing. Their technology transfer practices can

¹⁵⁰ Lydon et al. 2008. Vaccine.

¹⁵¹ Frew et al. 2006. Nature Biotech.

promote new channels for regional manufacturing while ensuring that licensing does not block pathways to low-cost regional manufacturing of existing vaccines. Therefore, these institutions should take notice of the novel licensing mechanisms set forth in the Association of University Technology Manager (AUTM)'s "9 Points."¹⁵² Furthermore, they should view DCVMs as equal partners in vaccine development collaborations. Considering them for initial licenses to new, enabling vaccine technologies could better facilitate regional vaccine manufacturing overall.

¹⁵² In the Public Interest: Nine Points to Consider in Licensing University Technology. 2007.

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APPENDICES

Appendix 1: Sample interview questions that will be altered slightly for each vaccine

Hepatitis B:

- When did you begin research on the Hepatitis B vaccine?
- Why did you choose the Hepatitis B vaccine?
- What kind of research collaborations were involved in the R&D for this vaccine?
- Who did you collaborate with?
- What was the nature of the collaboration?
 - (1) Information exchange?
 - (2) Biological materials?
 - (3) Personnel training exchange?
- What technology transfer partnerships (if any) did you initiate?
- What type of licensing agreements did you enter (if any)?
- How important was IP status in the decision to develop Hepatitis B?
- Did you have to do a freedom to operate (FTO) analysis or was that an issue at all?
- How long did it take to bring the Hepatitis B vaccine to market?
- What were your specific advantages in your ability to bring Hepatitis B to the market in comparison to other companies?
 - (1) Technology platform?
 - (2) Marketing practices/agreements?
- What kind of regulatory approval was required?
- Did you need to conduct clinical trials? If so, who funded them? Were they placebo controlled or imported vaccines?
- Did the imported vaccine present a barrier to entry?
- What about competition for other biotech companies in India?
- What is your market price?
- What is your annual revenue from the sale of Hepatitis B? Does it come from local or international markets?

HPV/Rotavirus:

- How and why did you choose the HPV/Rotavirus vaccine?
- How similar is the technology to Hepatitis B to translate onto your technology platform?
- What kind of research collaborations are involved in your R&D process?
- What is the nature of the collaboration?
 - (1) Information exchange?
 - (2) Biological materials?
 - (3) Personnel training exchange?
- What technology transfer partnerships have you entered or are planning to enter?
- Have you entered any licensing agreements, and do you plan to enter into more in the near future?
- How important was IP in your decision to choose the HPV/Rotavirus vaccine?
- Has IP in general limited your ability to experiment with HPV/Rotavirus technology?
- Have you done a FTO analysis?

- How long do you think it will take to bring a viable vaccine to market?
- Are there any obstacles in place either from the western world or within India itself that is inhibiting the R&D process?
- At what stage are you in developing an HPV vaccine?
- What advantages do you foresee of having an indigenous HPV vaccine as opposed to the ones made by Merck and GSK?