

Compulsory Licenses: A Tool to Improve Global Access to the HPV Vaccine?

Peter Maybarduk[†] & Sarah Rimmington^{††}

ABSTRACT

Cervical cancer disproportionately affects women in lower- and middle-income countries. But the new vaccines developed to prevent infection with some strains of the human papillomavirus (HPV) that cause cervical cancer are priced beyond the reach of most women and health agencies in these regions, due in part to the monopoly pricing power of brand-name companies that hold the patents on the vaccines. Compulsory licenses, which authorize generic competition with patented products, could expand access to HPV vaccines under certain circumstances. If high-quality biogeneric HPV vaccines can be produced at low cost and be broadly and efficiently registered, and if Merck and GSK are unwilling to grant licenses on a voluntary basis, compulsory licensing could play a pivotal role in ensuring vaccinations against HPV are available to all, around the world, regardless of ability to pay.

I. INTRODUCTION

Cancer is the third leading cause of female deaths worldwide and cervical cancer is the fifth deadliest form of cancer in women.¹ Every year about half a million women are diagnosed with the disease, and more than a quarter of a million die from it.² But the burden of cervical cancer is not shared equally among women from all corners of the globe. More than 85 percent of new

[†] J.D., University of California at Berkeley. Attorney, Essential Action, Access to Medicines Project.

^{††} L.L.B., University of Windsor; M.A., Columbia University, School of International and Public Affairs (SIPA). Attorney, Essential Action, Access to Medicines Project.

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¹ WORLD HEALTH ORGANIZATION (WHO), THE GLOBAL BURDEN OF DISEASE: 2004 UPDATE 8, 13 tbl. 3 (2008) [hereinafter Global Burden 2008].

² D. Maxwell Parkin & Freddie Bray, *Chapter 2: The Burden of HPV-Related Cancers*, 24 VACCINE (SUPP. 3) S11, S11 (2006).

cervical cancer cases occur in lower- and middle-income countries.³ Notably, cervical cancer is the leading cause of cancer deaths among women in the African and South East Asia regions, while it is the tenth most common cause of cancer deaths among women in high-income regions and countries like the United States, Canada, Japan, and the countries of the European Union.⁴ The extremely high morbidity from cervical cancer among women in the developing world is largely attributed to the absence of regular and effective pre-cancer screening and treatment services.⁵

The good news is that two recently developed vaccines appear, so far, to be highly effective at preventing infection with the two strains of the human papillomavirus (HPV) that cause 70 percent of cervical cancer.⁶ The bad news is that these vaccines, GlaxoSmithKline's (GSK) Cervarix® and Merck's Gardasil®, are much more expensive on average than other vaccines, and are too expensive to facilitate widespread global vaccination against HPV. The three-dose series of Gardasil costs \$360 in the United States and other industrialized countries. One study found that the vaccine would only be cost-effective in Brazil, an upper middle-income country, at a dramatically reduced price of \$25 per person. Countries where the per capita gross domestic product was less than \$1000 would require a price as low as \$3-\$6 per person to be cost-effective and affordable.⁷

³ Leslie Mancuso, *Cervical Cancer: An Overlooked Killer in Low-resource Countries*, PUMP HANDLE, Jan. 13, 2009, <http://thepumphandle.wordpress.com/2009/01/13/cervical-cancer-an-overlooked-killer-in-low-resource-countries/>.

⁴ *Global Burden 2008*, *supra* note 1.

⁵ See Emmanuela Gakidou et al., *Coverage of Cervical Cancer Screening in 57 Countries: Low Average Levels and Large Inequalities*, 5 PLOS MEDICINE 863, 863 (2008).

⁶ The U.S. Food and Drug Administration (FDA) first approved Merck's Gardasil® [Human Papillomavirus Quadrivalent Vaccine (Types 6, 11, 16, and 18) Recombinant] in June 2006. Marc Kaufman, *FDA Approves Vaccine that Should Prevent Most Cervical Cancers*, WASH. POST, Jun. 9, 2006, <http://www.washingtonpost.com/wp-dyn/content/article/2006/06/08/AR2006060800865.html>. The product is approved for the prevention of cervical, vulvar and vaginal cancers; genital warts; and precancerous or dysplastic lesions in girls and young women 9 through 26 years of age. Press Release, Merck, FDA Approves Merck's GARDASIL® to Protect Against Two Additional Cancers (Sept. 12, 2008), http://www.merck.com/newsroom/press_releases/product/2008_0925.html. GlaxoSmithKline's (GSK) product Cervarix® [Human Papillomavirus Vaccine (types 16, 18) Recombinant, Adjuvanted, Adsorbed] was first approved in Australia in March 2007 and the 27 member countries of the EU in September 2007. It is approved to prevent cervical, vulvar and vaginal cancers and precancerous or dysplastic lesions in girls and young women aged 15-25. Press Release, GlaxoSmithKline, Cervarix, GSK's Cervical Cancer Vaccine, Wins Tender for Dutch National Immunisation Programme (Nov. 20, 2008), http://www.gsk.com/media/pressreleases/2008/2008_pressrelease_10123.htm. HPV strains 16 and 18 are estimated to cause 70% of all cervical cancers. See e.g., Luisa L Villa et al., *Prophylactic Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-like Particle Vaccine in Young Women: A Randomised Double-blind Placebo-controlled Multicentre Phase II Efficacy Trial*, 6 LANCET ONCOLOGY 271, 271 (2005); F X Bosch et al., *The Causal Relation Between Human Papillomavirus and Cervical Cancer*, 55 J. CLINICAL PATHOLOGY 244, 248 (2002). Initial studies show that efficacy rates for both vaccines approach 100 percent if girls are inoculated prior to sexual debut. The duration of protection for both products is unknown. Diane M Harper et al., *Sustained Efficacy Up to 4.5 Years of a Bivalent Li Virus-Like Particle Vaccine Against HPV Types 16 and 18: Follow Up from a Randomized Controlled Trial*, 367 LANCET 1247, 1247 (2006).

⁷ HELEN SAXENIAN, PROGRAM FOR APPROPRIATE TECHNOLOGY HEALTH (PATH), HPV VACCINE ADOPTION IN DEVELOPING COUNTRIES: COST AND FINANCING ISSUES 8-11 (2007);

Other factors, including inadequate health financing and infrastructure, may also reduce access to the vaccines. But lowering prices is a necessary, if not sufficient, condition for improving access.⁸ Unless the HPV vaccines are made available at a significantly lower price to developing country procurement agencies and other purchasers, it is extremely unlikely they will become available to women in low- and middle-income countries on a widespread basis.

The high prices of the HPV vaccines are a result of the pricing decisions of GSK and Merck, the brand-name pharmaceutical companies that hold patent monopolies on the two new products. Governments confer patents – intellectual property rights to prevent others from using or selling a new technology for twenty years – in order to reward, and thus encourage, innovation.⁹ But when a patent gives a pharmaceutical company exclusive control of a medicine, prices start high, and generally stay high.¹⁰ Some people who cannot afford or access the vaccine will grow ill, and some will die. Fortunately, international law provides a safeguard, in the form of an underutilized tool called a compulsory license.

Compulsory licenses authorize price-lowering competition for products that remain on patent (also referred to as “brand-name” products), in exchange for a royalty payment to the patent holder. Under international law, either the authorizing government or a private company or organization may manufacture and provide a compulsorily licensed pharmaceutical product, and it may be manufactured for domestic use, imported, or, with certain conditions met, exported. Government programs, private sector pharmacies, or both, may supply the generic products to patients, depending on the terms of the compulsory license.

For example, in 2003, Malaysia issued government use compulsory licenses on three patented AIDS medicines, and began importing generic versions of the drugs from India.¹¹ The generics reduced the cost to the Malaysian Ministry of Health of treating an HIV/AIDS patient by 81 percent – from \$315 to \$58 per month. The savings enabled Malaysia to increase the number of HIV/AIDS patients it treated in government hospitals from 1,500 to 4,000.

There are many other examples. In recent years, Indonesia, Mozambique, Zimbabwe, South Africa, Eritrea and Zambia have each issued compulsory licenses to promote access to medicines.¹² Brazil, in addition to issuing a

Jan M. Agosti & Sue J. Goldie, *Introducing HPV Vaccine in Developing Countries – Key Challenges and Issues*, 356 *NEW ENG. J. MED.* 1908, 1909-10 (2007).

⁸ ELLEN F.M. 'T HOEN, *THE GLOBAL POLITICS OF PHARMACEUTICAL MONOPOLY POWER* 87 (2009).

⁹ For a basic overview of principles and international laws governing patents, see World Intellectual Property Organization (WIPO), *What is Intellectual Property?*, <http://www.wipo.int/about-ip/en/> (last visited Apr. 9, 2009).

¹⁰ Patents cause high prices sources. 'T HOEN, *supra* note 8.

¹¹ CHEE YOKE LING, *THIRD WORLD NETWORK, MALAYSIA'S EXPERIENCE IN INCREASING ACCESS TO ANTIRETROVIRAL DRUGS: EXERCISING THE "GOVERNMENT USE" OPTION* 5 (2006).

¹² For example, see JAMES PACKARD LOVE, *KNOWLEDGE ECOLOGY INTERNATIONAL, RECENT EXAMPLES OF COMPULSORY LICENSING OF PATENTS*, JAMES PACKARD LOVE 12 (2007), available at http://www.keionline.org/index.php?option=com_content&task=view&id=41&Itemid=1.

compulsory license on the AIDS drug efavirenz in 2007, negotiated discounts between 40 and 65 percent on nelfinavir, imatinib, efavirenz, tenofovir and lopinavir/ritonavir between 2001 and 2007 against the backdrop of threatening to issue compulsory licenses.¹³

Historically, the introduction of generic competition has been the most effective way to reduce the price of medicines. Typically, as the first generic competitors enter a market, prices fall, and continue to fall over time as more competitors enter. One study showed that after generic versions of medicines enter the U.S. market, prices fall on average between 40 and 80 percent, depending on the number of firms entering the market.¹⁴

Over the last ten years the world has witnessed a revolution in global HIV/AIDS treatment, with three million people gaining access mostly to the older first-generation treatments once priced far beyond people's and health agencies' ability to pay. Treatments that once cost over \$10,000 per person, per year, are now available in generic form for \$100, and sometimes less. The widespread availability of generic copies, and the effect of competition on brand-name prices, made this possible.¹⁵

Whether we are likely to see a similar pattern develop in HPV vaccine access may depend on whether effective alternatives to the Merck and GSK products – namely, biogenerics¹⁶ or second-generation vaccines¹⁷ – can be

¹³ *Id.* at 16-17.

¹⁴ UNITED STATES CONGRESSIONAL BUDGET OFFICE (CBO), HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 32 (1998), available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf>.

¹⁵ T HOEN, *supra* note 8, at 25.

¹⁶ The authors use the term “biogenerics” or “generic biologics” to include products that are determined to be “identical” and “therapeutically equivalent” by scientists, as well as products that are found to be “highly similar” and “comparable” (similar, comparable medicines are in the same product class and have the same therapeutic purpose, but the molecules cannot be scientifically characterized as identical and the product is not defined as therapeutically equivalent). Often a distinction is drawn between these two categories, with identical or equivalent products labeled “generics” or “biogenerics” and highly similar products called “biosimilars” or “follow-on biologics.” For the purposes of this paper and the sake of simplicity, the authors choose not to make a distinction between these two categories and to use the term biogenerics to refer to all of them.

Technology and regulatory pathways for both categories of product are still developing, and the authors acknowledge no one has yet engineered or registered generic copies of any vaccine, and that it may be quite difficult to do. But it is possible the scientific know-how and the regulatory environment will evolve in coming years such that it will be possible to engineer and market generic HPV vaccines, which would in fact be called “biosimilar” or “biogeneric” products. The specific challenges related to engineering and registering generic versions of biologic products like the HPV vaccine will be discussed in greater detail in the text and footnotes of Section III.

¹⁷ At least one Indian vaccine-maker, Shantha Biotechnics, is currently attempting to engineer a low-cost second-generation HPV vaccine. Second-generation products are not generic imitations or copies of the original first-generation product (in the case of the HPV vaccine there are two first-generation products, Merck's Gardasil and GSK's Cervarix). Because second-generation products are not generics, but are new and different product albeit with the same therapeutic purpose, they have to undergo the full battery of safety and efficacy tests of the relevant regulatory authorities before being approved for sale. There is no guarantee that Shatha will be successful at developing this product, which some have estimated is not likely to be ready for marketing – if at all – until 2015 or beyond. SAXENIAN, *supra* note 7, at 6-7; Gunjan Pradhan Sinha, Byline, *Shantha Developing \$15 Cervical Cancer Vaccine*, ECON. TIMES (INDIA), October 16, 2007.

introduced, creating competition. Merck and GSK may establish tiered pricing programs with somewhat lower prices for low-income markets, and other voluntary initiatives such as vaccine donation programs could expand access to the HPV vaccines.¹⁸ But donations will not satisfy global need, and voluntary price reductions rarely yield prices as low as competition can drive them. If competitive generic vaccines can eventually be produced, then competition will likely be the best way to generate low prices, and lower them further with time. Patent licensing – whether through voluntary agreements with Merck and GSK or compulsory licenses issued by governments – will authorize this competition.

Issuing compulsory licenses for domestic use is usually procedurally simple. The conditions required to issue licenses are occasionally exaggerated, due to both limited public understanding of the tool and the vested financial interests of major pharmaceutical firms. In fact, however, countries are free under World Trade Organization (WTO) rules to issue compulsory licenses at any time to protect public health.

Issuing licenses for export can be more complicated, and in the case of widely distributing generic HPV vaccines, would probably be necessary, as the vaccines are likely to be patented in potential manufacturing countries. The WTO maintains an export-licensing regime that many health advocates have criticized as needlessly complex.¹⁹ All the same, manufacturing countries and importing countries have the right to enter agreements and issue export compulsory licenses to address public health needs.²⁰

If manufacturing and registration issues can be resolved, and vaccine makers can offer generic vaccines at sufficiently low prices, compulsory licensing could be an important tool to facilitate widespread access to HPV vaccines in many developing countries. Lower prices would enable governments and humanitarian agencies to purchase far greater quantities of the vaccines, and vaccinate many more young adolescent girls against HPV.

Section II outlines the international legal basis for issuing compulsory licenses to promote access to generic medicines and vaccines in developing countries. Section III outlines two threshold questions – pertaining to patent status and vaccine availability – that must be addressed before a determination can be made as to whether compulsory licensing of the HPV vaccine is an appropriate tool to promote generic competition. Section IV provides a how-to guide to assist developing countries in issuing compulsory

¹⁸ To learn more about other types of access initiatives *see generally* Colleen V. Chien, *HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare?* 3 PLoS ONE e278 (2007), P.J. Hammer, *Differential Pricing of Essential AIDS Drugs: Markets, Politics and Public Health*, 5 J. INT'L ECON. L. 2158 (2002), Kevin Outterson & Aaron S. Kesselheim, "Market-Based Licensing for HPV Vaccines in Developing Countries," 27 HEALTH AFFAIRS 130 (2008); Press Release, Médecins sans Frontières, Gilead's Tenofovir Access Program for Developing Countries: A Case of False Promises? (Feb. 7, 2006), http://www.msfaaccess.org/media-room/press-releases/press-release-detail/?tx_ttnews%5Btt_news%5D=31&cHash=65d72b8994.

¹⁹ *See, for example*, Essential Action, Statement on Paragraph 6 Deal, Dec. 6, 2006, <http://www.essentialaction.org/access/index.php?/archives/46-Statement-on-Paragraph-6-Deal.html>.

²⁰ *See, for example*, Essential Action, The WTO: Areas of Concern, and What We are Doing, <http://www.essentialaction.org/access/index.php?/archives/49-The-WTO-Areas-of-Concern,-and-What-We-Are-Doing.html>.

licenses for domestic production, import or export of generic HPV vaccines, and addressing common challenges that arise during this process. We believe the analysis in Section IV is also useful as a guide for the compulsory licensing of other medical products.

II. THE INTERNATIONAL LEGAL BASIS FOR COMPULSORY LICENSES

The WTO's 1995 Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) and the 2001 WTO Doha Declaration on the TRIPS Agreement and Public Health guarantee that, under international law, all WTO member countries have the right to issue compulsory licenses on patented medicines and other health-related inventions.²¹

The TRIPS Agreement requires all 151 WTO member countries²² to adopt strict U.S.-style patent rules for all products, including pharmaceuticals. Prior to the adoption of TRIPS, many countries – in particular developing countries – did not issue or enforce product patents or limited patent holders' rights on essential goods like medicines and food, because patents on these types of goods were widely seen as being against the public interest. Despite serious reservations about adopting a U.S.-style patent regime, developing countries agreed to adopt TRIPS in exchange for the public health guarantees included in the agreement, including the right to issue compulsory licenses allowing import or domestic production of generic medicines.²³ TRIPS also created a significant problem by limiting the rights of countries and generics firms to export drugs manufactured under compulsory license. TRIPS initially required licenses to be issued primarily to serve the domestic market (a requirement since waived with imperfect but workable export procedures). Such a limitation could render local production of a generic drug uneconomical even if it would be legally permissible to do so. Without economies of scale – often created by the availability of export markets – it would not be economically feasible to produce a generic drug.²⁴

Following the adoption of TRIPS in 1995, the novelty of the agreement and its hard-to-understand text left developing countries uncertain of their right to promote access to essential medicines. Clearly, there were conflicting understandings as to how developing countries could implement the sections relating to pharmaceutical patents, and several high profile trade disputes arose between wealthy and developing countries when the latter tried to adopt or use seemingly TRIPS-compliant measures to lower medicine prices.²⁵

²¹ Agreement on Trade-Related Aspects of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, art. 9, Apr. 15, 1994, 33 I.L.M. 81, available at http://www.wto.org/english/docs_e/legal_e/27-trips.pdf [hereinafter TRIPS].

²² For a list of WTO member countries, see World Trade Organization, Understanding the WTO: The organization, http://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm (last visited Apr. 10, 2009).

²³ See, TRIPS *supra* note 21, art. 31.

²⁴ 'T HOEN, *supra* note 8, at 35.

²⁵ For example, in 1998, a coalition of pharmaceutical companies sued South Africa, alleging that its newly inaugurated Medicines Act, which permitted price-reducing, access-promoting practices such as parallel importation and compulsory licensing, violated TRIPS. Public resistance and poor legal bases for these claims prompted the pharmaceutical

The WTO's unanimous 2001 Doha Declaration made it absolutely clear that developing countries have the right to use compulsory licensing and other flexibilities to promote public health under TRIPS. Specifically, Paragraph Four of the Declaration affirms that WTO members may use "to the full" the flexibilities in the TRIPS Agreement "to protect public health and, in particular, to promote access to medicines for all." Paragraph Five of the Declaration laid out the key measures and flexibilities provided by TRIPS, including that each member country "has the right to grant compulsory licenses and the freedom to determine the ground upon which such licenses are granted."²⁶

The Doha Declaration also created new rights for the poorest developing countries by allowing those categorized as Least-Developed Countries (LDCs) to delay the introduction or enforcement of pharmaceutical patents and the protection of undisclosed test data until at least 2016. Member countries failed, however, to resolve the question of whether and how to permit the production of generics for export under compulsory license.

Member countries attempted to resolve the compulsory license for export question two years later. An August 30, 2003 order of the WTO General Council waived the requirement that drugs manufactured under compulsory license be primarily for the domestic market when certain procedural requirements are met.²⁷ The procedural requirements, and common challenges that arise when issuing compulsory licenses, will be discussed in more detail in Section IV of this paper.

In spite of the Doha Declaration and increasing use of compulsory licenses, the brand-name pharmaceutical industry and a number of individuals and interest groups – some of whom have undisclosed ties to the industry²⁸ – oppose the issuance of compulsory licenses by developing

manufacturers and United States to abandon this case. But this and other incidents underscored lingering conflicting understandings of TRIPS within the international community. *See generally* Robert Weissman, *Aids Drugs for Africa: Grassroots Pressure Overcomes U.S.-Industry "Full Court Press" to Block South Africa's Affordable Medicine Program*, 20 MULTINATIONAL MONITOR 9 (1999), available at <http://multinationalmonitor.org/mm1999/99sept/aids.html>.

²⁶ Declaration on the TRIPS Agreement and Public Health, WT/MIN(01)/DEC/2, para. 5b, 41 I.L.M. 755 (2002) [hereinafter Doha Declaration].

²⁷ Paragraph 6 of the Doha Declaration recognized this burden on countries' compulsory licensing rights, and instructed the TRIPS Council to "find an expeditious solution." Doha Declaration, *supra* note 26, para. 6. On August 30, 2003, the WTO General Council responded with an implementing decision that indefinitely waives TRIPS article 31(f) for pharmaceutical patents, subject to certain limitations and labeling requirements. WTO, Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health (Sept. 1, 2003), http://www.wto.org/English/tratop_e/trips_e/implement_para6_e.htm. WTO members have since agreed on a TRIPS amendment that will make this waiver permanent, and will enter into force upon ratification by two-thirds of the members. Press Release, World Trade Organization, Members OK amendment to make health flexibility permanent (December 6, 2005), http://www.wto.org/english/news_e/pres05_e/pr426_e.htm. Public health advocates argue that the "Paragraph 6 solution" is too procedurally onerous to be effective, and that a simpler solution should be put into place. Consumer Project on Technology, *Joint NGO Statement on TRIPS and Public Health WTO Deal on Medicines: A "Gift Bound in Red Tape"* (September 10, 2003), <http://www.cptech.org/ip/wto/p6/ngos09102003.html>.

²⁸ Essential Action, Robert Weissman, Letter to the Editor submitted to the BANGKOK POST by Robert Weissman, Bangkok Post Letter: Commentator

countries, and in particular by middle-income developing countries like Thailand and Brazil. These actors sometimes mistakenly contest the scope of compulsory licensing rights or misrepresent the factual details surrounding the issuance of compulsory licenses.

For instance, after Thailand issued three compulsory licenses for two newer HIV/AIDS treatments and one treatment for heart disease in late 2006 and early 2007 in order to provide these drugs to the poor within its much-lauded public health system, individuals, interest-groups and even some U.S. congressmen, portrayed Thailand as having violated several TRIPS requirements. The inaccurate arguments against Thailand's actions included that the licenses were unlawful because compulsory licenses should only be issued in cases of public health emergency, and that compulsory licenses should be limited to drugs for HIV/AIDS and other communicable diseases.²⁹ But TRIPS does not limit the grounds on which compulsory licenses may be issued or the health problems for which compulsory licenses can be used.³⁰ Moreover, governments in many countries use compulsory licenses frequently for a wide variety of products, including but not limited to medicines, and in a wide variety of circumstances.³¹ For example, in 2006 alone, at least four U.S. courts issued compulsory licenses on medical, software and engineering patents to remedy anticompetitive business practices.³²

III. THRESHOLD QUESTIONS

Resolving two threshold questions would reveal whether compulsory licensing is a useful tool for improving access to the HPV vaccines. Namely: are the vaccines patented in potential generic vaccine manufacturing and

an Advisor to Law Firm that Represents Big Pharma, (May 11, 2007), <http://www.essentialaction.org/access/index.php?/archives/96-Bangkok-Post-Letter-Commentator-an-advisor-to-law-firm-that-represents-Big-Pharma.html>; Robert Weissman, *Compulsory Licenses the Right Medicine for Prescriptions in Developing Countries*, S. FLA. SUN-SENTINEL, March 18, 2008; Robert Weissman, *Ken Adelman's (New Lies)*, HUFFINGTON POST, May 7, 2007; Robert Weissman, *Stronger Patent Protections Will Take Lives, Not Save Them*, RIVER CITIES' READER (Iowa), March 19, 2008; Shaun Zeller, *The Shadowy Drug Lobby that Has Thailand in Its Sights*, CQ WKLY., May 14, 2007, <http://www.essentialaction.org/access/index.php?/archives/105-The-Shadowy-Drug-Lobby-That-Has-Thailand-in-Its-Sites.html>.

²⁹ To read more about the opposition to the Thai compulsory licenses and related issues see, for example, Brook Baker, *The Eight Deadly Lies of Big Pharma*, NATION (THAIL.), April 21, 2007; Professor Brook K Baker et al., Letter to the Editor, *Article Misleads in Support of Big Pharma*, BANGKOK POST, April 26, 2007, available at <http://www.essentialaction.org/access/index.php?/archives/58-Bangkok-Post-letter-Abbotts-law-firms-deceptions.html>; Daniel Ten Kate, *US-Thailand Dispute over Compulsory Licenses for AIDS Drugs*, ASIA SENTINEL, May 9, 2007; Letter from Senator Joseph Lieberman et al. to United States Trade Representative (USTR) Susan Schwab (March 20, 2007), <http://www.cptech.org/ip/health/c/thailand/>.

³⁰ For an example, see TRIPS, *supra* note 21, art. 31; WTO, TRIPS and Health: Frequently Asked Questions, Compulsory Licensing of Pharmaceuticals and TRIPS (September 2006), http://www.wto.org/english/tratop_e/TRIPs_e/public_health_fa_q_e.htm.

³¹ For a partial global list of compulsory licenses, see LOVE, *supra* note 12, at 2.

³² *Id.* at 5. The United States also threatened to issue a compulsory license on Tamiflu unless Roche produced it in the United States (Roche complied). *Id.* at 3. As early as 1952, the U.S. Supreme Court granted the "well-recognized remedy" of compulsory licenses in antitrust actions. *United States v. Besser Mfg. Co.*, 343 U.S. 444, 447 (1952).

importing countries, and are vaccine manufacturers willing and able to produce and broadly register generic HPV vaccines?

Compulsory licensing reduces prices and improves access by introducing generic competition where products are patented. Hence, if products are not patented, compulsory licenses are not necessary. The patent landscape in smaller developing countries remains unclear, but it is probable the HPV vaccines are patented in the major potential manufacturing countries (such as India or the European Union member states).³³ These countries often represent sizeable domestic markets and, through exports, even larger markets, which brand-name companies have strong financial interests in defending through patent protection. Unless a major supplier country could be identified where the vaccines are not patented, compulsory licensing would probably be a necessary component of a generic competition-based access strategy.

The second threshold question is whether manufacturers are able and willing to produce and distribute generic versions of the HPV vaccine on an appropriate timetable. The purpose of issuing a compulsory license is to introduce price competition while a product remains under patent. Thus if no companies are willing or able to make and distribute generic versions of the HPV vaccine before patents expire,³⁴ compulsory licensing will not be the correct tool to improve access. Answering this question involves several issues.

A critical, and perhaps impermeable, barrier is that no vaccine maker in the world has yet developed a generic version of either HPV vaccine, and it is unclear whether it will be possible to do so in the near future. The challenges are both scientific and regulatory, and are linked to the fact that vaccines are biologics, a category of products that are different from traditional chemical drugs in important ways. Biologics – also known as biotech drugs – are made from living organisms or the products of living organisms, and are generally more complex to characterize and to manufacture than traditional chemical drugs. The biotech drug industry is also relatively new compared to that of conventional pharmaceuticals, with most products having been developed since the 1980s.

Because of the differences between traditional chemical drugs and biologics and the relative youth of the biotech industry, it was only recently that countries began to consider developing approval processes for generic versions of biologics.

For traditional chemical drugs (also called “small molecule” drugs), generic drug companies do not repeat the extensive clinical tests performed by the brand-name companies to demonstrate safety and effectiveness and gain marketing approval for their products from drug regulatory agencies like the U.S. Food and Drug Administration (FDA). Instead, they follow an abbreviated process featuring bioequivalence tests that show their product is chemically identical to the original drug, and that it works the same in the body. Then the generics companies rely on the drug regulatory agency’s approval of the brand-name product to earn approval for their generic version.

Different procedures are required to demonstrate the safety and efficacy of

³³ Patents in some of these countries are listed in the online databases referenced *infra* Section IV.

³⁴ See note 57 for some information on projected expiration dates of the HPV vaccine patents.

most biogenerics³⁵ because the bioequivalence tests used for traditional chemical drugs are not appropriate for most biologics. Additional or different clinical trial data will be necessary to address the safety and efficacy concerns specific to generic biologics. Regulators have begun to address the lack of abbreviated approval pathways for generic biologics in recent years. In 2003, the European Union introduced the first biogenerics regulatory system.³⁶ Canadian regulators approved that country's first ever biogeneric product on April 20 2009,³⁷ and the United States Congress is currently discussing the terms of its own proposed abbreviated biologics approval process.³⁸

Discussions surrounding these regimes to date have focused on therapeutic protein products, which are but one of several categories of biologic drugs. The focus on therapeutic proteins stems from the fact that they are the only category of biologic for which the scientific know-how currently exists to immediately establish abbreviated safety and efficacy tests. Such procedures have not yet been developed for several other categories of biologics, including vaccine products. It is possible, however, that these procedures will be developed over time, and even in the near future. Large numbers of drug companies, including both brand-name and generics companies, large and small, those traditionally focused on biotech products and those traditionally focused on conventional pharmaceuticals, are rapidly expanding into both biologics and biogenerics. In fact, both innovative and generic biotech drugs are widely viewed as the future of the pharmaceutical industry, as pipelines for conventional pharmaceuticals have largely dried up and innovation in the much younger biotech sector is exponentially expanding.³⁹ Also, as more and more large, high-income countries, in

³⁵ See note 16 for the authors' discussion of the term "biogeneric."

³⁶ The European Medicines Evaluation Agency (EMA), located in London, authorizes marketing of conventional drugs and biologics throughout the European Union (EU) on the basis of a single application. In 2003, the EU passed legislation allowing for the sale of what it calls "biosimilars." The legislation became effective in 2005. EMA has approved five biogenerics (called "biosimilars" in their legislation) since 2004, including competitors with Johnson & Johnson's Eprex and Amgen's Neupogen. For more information, see European Medicines Evaluation Agency (EMA), <http://www.emea.europa.eu/> (last visited Apr. 13, 2009).

³⁷ Press Release, Canadian Generic Pharmaceutical Association, First Subsequent Entry Biologic Approved in Canada (Apr. 23, 2009), http://www.canadiangenerics.ca/en/news/apr_23_09.asp, For information on the Canadian rules, see the Health Canada Biologics, Radiopharmaceuticals and Genetic Therapies webpage at <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php> and Ogilvy Renault, *Health Canada issues revised draft Guidance Document for Subsequent Entry Biologics*, March 31, 2009, http://ogilvyrenault.com/en/resourceCentre_9170.htm.

³⁸ The U.S. Congress is currently debating several proposals that would result in the introduction of a regulatory approval process for biogenerics. Many expect the legislation to pass by late 2009 or 2010. See John Carroll, *Biosimilar Bill Offers 12 Years of Market Exclusivity*, FIERCE BIOTECH, Mar. 18, 2009, <http://www.fiercebitech.com/story/new-biosimilar-bill-offers-12-years-market-exclusivity/2009-03-18>; Lewis Krauskopf, *Teva Executive Upbeat on Biogenerics in 2009*, REUTERS, Dec. 23, 2008, <http://www.reuters.com/article/ousiv/idUSTRE4BM4OA20081223>; Lisa Richwine, *U.S. Lawmakers Propose Generic Biotech Drug Plan*, REUTERS, Mar. 11, 2009, <http://www.reuters.com/article/latestCrisis/idUSN11301138>.

³⁹ See for example, Bill Berkrot & Ransdell Pierson, *Lilly Eyes Entry into Biogenerics Arena*, REUTERS, Dec. 11, 2008, <http://www.reuters.com/article/rbssHealthcareNews/idUSN1138748320081211>; John Carroll, *Biotech Buyout Spree Ahead as Values Crumble*, FIERCE BIOTECH, Jan. 6, 2009,

particular the United States, adopt regulatory regimes for the approval of safe and effective biogenerics, significantly increased investments of time and capital will likely be directed at developing a variety of biogenerics, possibly including a copy of a first-generation HPV vaccine. More concretely, an analysis in this very publication suggests that a promising approach to demonstrate the safety and efficacy of generic copies of vaccines already exists.⁴⁰ In this context, it would not be surprising if the ability to produce generic HPV vaccines were to develop quickly, especially if it was perceived that the markets for them would be sufficiently large to be cost-effective.

It is important to note, however, that it is not yet clear whether the abbreviated regulatory procedures for biogenerics under discussion in the United States will leave the door open to approve biologic products like vaccines, for which new and different and yet-to-be developed abbreviated safety and efficacy tests will be required.⁴¹ Given the nature of the debate surrounding the legislation in the United States in particular, it is possible that the regime put in place will circumscribe the regulatory process in ways that limit the types of products that can be approved. If legislators instead give drug regulators the discretion to vary the abbreviated approval procedures for determining the safety and efficacy of generic vaccines and other categories of biologics as scientific advancement occurs, it will be possible to register biogeneric versions of products like the HPV vaccine.

Even if the scientific and regulatory issues are resolved quickly enough for a generic HPV vaccine to be possible in the next few years, generic vaccines still might not be made available to developing countries wishing to introduce them under compulsory license while the brand-name product remains under patent. This is because the global vaccine market, including markets in lower- and middle-income countries, is dominated by the large, brand-name pharmaceutical companies headquartered in high-income countries, although there are vaccine manufacturers in countries like India. The large pharmaceutical companies dominating the market are much more likely to possess or be able to quickly develop the know-how and capacity to develop generic versions of HPV vaccines than vaccine makers based in the developing world. The challenge associated with the primary control of the vaccine

<http://www.fiercebiotech.com/story/biotech-buyout-spree-ahead-values-crumble/2009-01-06>; Ransdell Pierson, *Merck CEO Says Biotechs a Buying Opportunity*, REUTERS, Oct. 22, 2008, <http://www.reuters.com/article/euPrivateEquityNews/idUSTRE49L83L20081022>; Barbara Martinez & Jacob Goldstein, *Big Pharma Faces Grim Prognosis*, WALL ST. J., Dec. 6, 2007, available at http://online.wsj.com/public/article_print/SB119689933952615133.html; Lina Saigol & Andrew Jack, Financial Times, *Pharma Spending Spree Could Swallow Biotechs*, GULF NEWS, Jan. 6, 2009, http://www.gulfnews.com/BUSINESS/Business_Feature/10272938.html; Aaron Smith, CNNMoney.com, *Big Pharma Blurring the Lines with Big Biotech* (May 29, 2007), <http://money.cnn.com/2007/05/25/news/companies/biotech/index.htm>.

⁴⁰ Sara E. Crager et al., *University Contributions to HPV Vaccines and Implications for Access in Developing Countries: Potential Models for Improving Access to University Discovered Vaccines*, 35 AM. J. L. & MED. 253 (2009).

⁴¹ The authors are also not certain if the Health Canada and EMEA guidelines would permit regulators the necessary discretion to vary the abbreviated approval procedures for determining the safety and efficacy of vaccines and other categories of biologics as scientific advancement occurs. A more thorough analysis of the guidelines would have to be conducted to draw any conclusion. EMEA, Human Medicines, <http://www.emea.europa.eu/index/indexh1.htm> (last visited Apr. 14, 2009).

market resting with these companies is that they have demonstrated widespread resistance to the compulsory licensing of medicines under similar circumstances in the recent past. None are likely to willingly supply generic HPV vaccine authorized under a compulsory license, in particular to middle-income countries with large enough markets to provide the economies of scale necessary to make generic production economically viable.

Thus even if the previous hurdles are surmounted, the feasibility of compulsory licensing as a tool to promote developing country access to generic HPV vaccines likely rests on whether generic drug-makers that would more likely be willing to supply generic HPV vaccines under compulsory license develop manufacturing capacity. One sign that this could be possible is that several Indian generic manufacturers have announced plans to enter the biogenerics market in the near future.⁴²

It is also possible that government manufacturing, or public-private partnerships, perhaps between some combination of universities, governments, foundations and generics manufacturers, might assist and encourage the development of manufacturing capacity in developing countries. Notably, if the public health community demonstrates a commitment to opening markets for generics firms – through, for example, broad expressed interest in compulsory licensing – this could provide valuable added financial incentive to generics manufacturers to invest in developing the capacity.

If generic pharmaceutical companies can develop an HPV vaccine, compulsory licensing of the patents by developing countries could be a valuable strategy to open markets to generic firms, providing incentives to scale-up manufacture, and allowing public health agencies and other relevant actors to widely distribute the vaccines. Meeting these threshold tests will be challenging and complex. But it is conceivable the difficulties outlined could be overcome, especially given regulatory approval processes for generic versions of biologic products such as vaccines are about to become more widespread, much more research and development (R&D) is sure to be invested in creating biogenerics, and many new biogeneric products will be brought to market.

IV. HOW TO ISSUE COMPULSORY LICENSES FOR HPV VACCINES

This Section provides a how-to guide; detailing step-by-step how governments and public health advocates can identify and clear the legal hurdles to bring potentially low-cost, high-quality HPV vaccines from manufacture in one country to market in another, including issuing compulsory licenses if needed. While this analysis is tailored to HPV vaccines, the steps and some of the lessons noted apply to other pharmaceutical products as well. Therefore, this Section may also be useful as a broader how-to guide for the compulsory licensing of medical products.

⁴² See Eric S. Langer, *Indian Biogenerics: An Evolving Industry*, *BIOPHARM INT'L* February 1, 2008, <http://biopharminternational.findpharma.com/biopharm/India+Today/Indian-Biogenerics-An-Evolving-Industry/ArticleStandard/Article/detail/490805>.

The HPV vaccines are most likely patented where generic or second-generation vaccines could be manufactured. Hence it will probably be necessary to issue compulsory licenses to authorize production and export, in order to supply countries with smaller markets or limited manufacturing capacity. It will be essential to assure the vaccines' quality, and legally required to demonstrate their safety and efficacy before the drug regulatory authority of any country wishing to use the vaccine. Health advocates must learn if the vaccines are patented in the importing country. If not, generics firms are free to sell, and governments and humanitarian organizations free to distribute the vaccine. If the vaccines are patented (and assuming generic or second generation vaccines rely on the patented technology), advocates and health officials could learn the domestic compulsory licensing laws and regulations, develop stakeholder support, request Merck and GSK openly license their vaccines voluntarily and, if they decline or do not respond, issue open compulsory licenses authorizing use of the vaccine technology. If the vaccines are widely patented around the world, access advocates might consider requesting global licenses of Merck and GSK, and again, if they decline or do not respond, support these steps in multiple countries. Finally, advocates should follow up to ensure the license is used, and the vaccine widely available at ever lower costs.

A. EXPORT LICENSES

Assuming generics firms, governments or partnerships succeed in making generic HPV vaccines; manufacturing is likely to be concentrated, at least initially, in a very few countries, or perhaps only one. Most developing countries will need to import the product. When many key first-generation AIDS treatments entered the market, some generics-manufacturing countries, such as India, were not yet subject to TRIPS patent rules.⁴³ Thus Indian firms have been able to manufacture generic versions of the older AIDS drugs for export without issuing compulsory licenses.⁴⁴

The case is likely to be different for the HPV vaccines. Today, India and other potential manufacturer countries are subject to TRIPS patent rules. The HPV vaccines are probably patented in these countries.⁴⁵ Hence, a compulsory license may be needed to export the vaccines from the manufacturer, and a second license may be needed to use the vaccines in the importing country.

Compulsory licenses for export can be issued if the manufacturing country has adopted legislation to implement the WTO's August 30 decision.⁴⁶ As was previously mentioned, this decision allows waiver of the requirement in Article 31 of TRIPS that products produced under compulsory license must be predominantly used to supply the domestic market. The process set out in the

⁴³ India amended its patent rules to comply with TRIPS in 2006.

⁴⁴ In some cases, the importing countries have had to issue licenses for domestic use, because the product was patented in their country. Remember, patent regimes are national. A product may be on patent in one country and not in another. WIPO, Frequently Asked Questions, http://www.wipo.int/patentscope/en/patents_faq.html#worldwide_patent (last visited Apr. 30, 2009).

⁴⁵ See note 35 and accompanying text.

⁴⁶ Doha Declaration, *supra* note 28, para. 6.

August 30 decision has been criticized as needlessly complex,⁴⁷ making difficult the attainment of the economies of scale necessary to stimulate the production of lower-cost generics. This is because the waiver does not simply allow manufacturing countries to choose which drugs they would be able to produce, and to make arrangements to export them to several countries. Instead, the mechanism has to be “invoked on a drug-by-drug, case-by-case, country-by-country basis.”⁴⁸

Regardless, at least five countries with export capacity have to date implemented such legislation. Some of these countries have gone further than TRIPS, limiting the scope of diseases and products for which the mechanism may be used, and one added additional procedural requirements.⁴⁹ Countries interested in potentially exporting or importing generic HPV vaccines should adopt this “Paragraph 6” implementing legislation.

Potential importing countries should first determine which, if any, eligible exporting countries are willing and able to export generic HPV vaccines in sufficient quantities at acceptable prices. The importing country must then officially notify the TRIPS Council of its desire to import from an eligible exporting country. According to Paragraph 2(a) of the decision, the notification to the Council must specify the names and expected quantities of the product or products needed over a specific period of time, and certify that if the products are under patent in the importing country that it has or will grant a compulsory license for import in accordance with Article 31 of TRIPS. Details about how to issue compulsory licenses for import will be discussed in the pages that follow. All importing countries except those that meet the WTO definition of least-developed country (LDC) must also outline the evidence that they have no or insufficient manufacturing capacity to produce the products in question in this notification.

The next step is for the exporting country to issue a compulsory license for the manufacture of the drug, and to notify the TRIPS Council of its issuance. The license must comply with its own specific national laws regarding compulsory licensing, if any, and they must meet the specific Paragraph 6 requirements. In particular, the license must specify the amount of the product that will be provided to the importing country, and the royalty rate that the importer will be paying.

Rwanda and Canada became the first countries to use the export mechanism in 2007. The countries agreed to export a patented HIV/AIDS drug combination, lamivudine/zidovudine plus nevirapine, from the private-

⁴⁷ See note 29.

⁴⁸ T HOEN, *supra* note 8, at 36.

⁴⁹ T HOEN, *supra* note 8, at 35-38. Examples of countries that have implemented export legislation, and in some cases to see the text of the legislation, are *available at* Legislation to Allow for the Export of Pharmaceuticals Produced Under Compulsory License, <http://www.cptech.org/ip/health/cl/cl-export-legislation.html> (last visited Apr. 14, 2009).

sector, Canada-based generic drug company Apotex to Rwanda.⁵⁰ Rwanda expects to import 260,000 packs over two years.⁵¹

B. VACCINE REGISTRATION

It is critical to ensure generic versions of the HPV vaccine are not only available and affordable, but also high quality. As described above in Section III, vaccine manufacture includes unique challenges, and only a limited number of firms make vaccines. In addition, health advocates should plan ahead for potential obstacles to registering the vaccines with national drug regulatory authorities – that is, earning government permission to distribute the vaccine by proving it is safe and effective. Any strategy to improve access through generic vaccines must account for registration hurdles.

Assuming pathways to generic vaccine approval are put in place,⁵² other important potential obstacles to efficient global registration include patent linkage and data exclusivity. It seems possible the WHO might prequalify generic HPV vaccines, and that manufacturers in countries that have previously registered vaccines for prequalification, including Brazil, India and Cuba, among others, could facilitate timely global registration.⁵³ Additionally, approval at the European Medicines Evaluation Agency (EMA) could be a gateway to global registration, if health officials seek a compulsory license for data.

Drug regulatory authorities in less populous developing countries generally do not have resources comparable to the U.S. FDA. Governments may require proof drug makers have followed good manufacturing practices, and may test the medicines actually brought to market to ensure they are precisely what they purport to be.⁵⁴ But if they do not have the capacity to independently assess all clinical data, they may instead rely on approval by the FDA, EMA, other major national regulatory authorities or the World Health Organization's prequalification program⁵⁵ as proof of a medicine's safety and

⁵⁰ Rwanda's notification to the TRIPS council can be downloaded at WTO, TRIPS: Trips Public Health 'Paragraph 6' System, Notifications by Exporting WTO Members, http://www.wto.org/english/tratop_e/trips_e/public_health_notif_export_e.htm (last visited Apr. 14, 2009).

⁵¹ Int'l Ctr. for Trade & Sustainable Dev., *Canadian WTO Notification Clears Path for Rwanda to Import Generic HIV/AIDS Drug*, BRIDGES WKLY. TRADE NEWS DIG., October 10, 2007, at 7-8, available at <http://ictsd.net/i/news/bridgesweekly/6568/>.

⁵² See Section III, *supra*.

⁵³ See notes 58-59 and accompanying text.

⁵⁴ Some countries may also have regulations making it difficult to register a follow-on drug if the original is not domestically registered. But Gardasil was already registered in 106 countries as of October 2008, with another 30 registrations pending; hence this should not be a significant barrier. See Press Release, Merck, FDA Approves Merck's GARDASIL® to Protect Against Two Additional Cancers (September 25, 2008), available at http://www.merck.com/newsroom/press_releases/product/2008_0925.html. As of September 25, 2008 Cervarix had been approved in more than 80 countries. Marketing applications have been submitted in more than 30 additional countries. GSK is still awaiting U.S. Food and Drug Administration (FDA) marketing approval for Cervarix™, which it applied for in March 2007. See Press Release, Glaxo Smith Kline, Cervarix, GSK's cervical cancer vaccine, Wins Tender for Dutch National Immunisation Programme (November 20, 2008), available at http://www.gsk.com/media/pressreleases/2008/2008_pressrelease_10123.htm.

⁵⁵ Information about the World Health Organizations' Prequalification Program is available at WHO, Prequalification Programme: A United Nations

efficacy (perhaps this dynamic will be especially pronounced in the case of generic biologic vaccines, given their unique manufacturing challenges). In cases of very important medicines, some small regulatory agencies may accept a variety of international quality indicators, provided they are reputable. But approval by major regulatory agencies or prequalification can be central to efficient registration, and hence, vaccine distribution, around the globe.

To begin, as was discussed in Section III, regulatory pathways to biogeneric approval at the major regulatory agencies are new (in the case of Europe) or, as of this writing, still in development (as in the USA), and it is not yet clear to what extent generic HPV vaccines would be able to take advantage of these pathways. To win approval at the major regulatory agencies that have yet to introduce an effective pathway, generic vaccine makers may need to present complete original clinical data as though they were introducing entirely new vaccines. This may be cost prohibitive.

Additionally, at some agencies including the FDA, regulatory approval is linked to patent status. This “linkage”⁵⁶ means generics most often cannot receive marketing approval until after patents expire (though they are usually free to begin product development). The Merck and Gardasil vaccines will be on patent for several years.⁵⁷ Even if makers of generic HPV vaccines are able

Programme Managed by WHO, <http://healthtech.who.int/pq/> (last visited Apr. 14, 2009). Information about vaccine prequalification is available at WHO, A System for the Prequalification of Vaccines for UN Supply, http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/index.html (last visited Apr. 14, 2009).

⁵⁶ In countries with linkage rules (such as the United States), the drug regulatory authority will not approve a drug for sale if another party claims a patent on it. Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301, 355, 360cc (1994); Creation of Remedy, 28 U.S.C. § 2201 (1994); Issue of Patents, 35 U.S.C. §§ 156, 271, 282 (1994)). In other words, under linkage, a drug generally must be off patent before generics can be sold. A compulsory license in a linkage system would allow the regulatory authority to approve a generic drug for sale in spite of a patent.

In countries without linkage, the drug regulatory authority gauges only safety and efficacy. If a drug works safely for its intended purpose, it may be sold on the national market. Drug companies enforce their patents through the courts or other dispute systems (in much of Latin America, patent holders file *medidas cautelares*), but not necessarily before a generic drug reaches market. In countries without linkage, generics may be found on the market even though a patent is claimed. Generics on the market may mean the drug is not patented, or that the patent holder has not filed suit to remove the generics, or that the claimed patent is actually weak or invalid. A compulsory license in a system without linkage would protect generics already on the market, and generics that might come on the market later, from enforcement actions brought by the patent holder.

A compulsory license provides generics companies, patients and government agencies security, ensuring a patent holder will not be able to force the generic off market after patients and agencies have come to rely on its low prices. This security may also act as an incentive to attract more generics firms to market. Drug registration, marketing and distribution are expensive for low-capitalized generics firms, and firms may prefer to avoid the risk if a drug is on patent, particularly in smaller countries where there is less potential profit to be made. Compulsory licenses assure generics firms their investment will be protected.

⁵⁷ According to the Health Canada and European government patent databases, some HPV patents may expire as early as 2012, but others are slated for 2016. For a general search of Canadian and European patent databases, see Canada, Patent Register Search Page, <http://www.patentregister.ca> (last visited Apr. 30, 2009); European Patent Office, About Patent Information, <http://www.epo.org/patents/patent-information/about.html> (*see infra*

to develop their products earlier and a pathway is put in place, they may still have to wait years until they could use FDA approval to assist widespread acceptance of their products.⁵⁸

There is one further wrinkle. Some authorities, including the United States and Europe, have data exclusivity laws that delay registration of generics. Data exclusivity prohibits generics firms from relying on the first drug or vaccine's data to prove the generic's equivalence for a period of years. This means even with effective pathways to generic vaccine approval in place, generic vaccine makers would still have to present original clinical data until data exclusivity expires. Again, this might prove cost prohibitive.

The new U.S. biogenerics legislation will likely include a data exclusivity period. We do not yet know how long it will be, nor do we know if it might apply retroactively to Gardasil, or if Cervarix will enter the market after the legislation is passed and qualify for the new exclusivity period automatically. New drugs in Europe are protected by ten years data exclusivity after the product receives marketing approval.⁵⁹ Data exclusivity could therefore prevent biogenerics from registering in Europe and the U.S. until a date even later than patent expiration, and consequently, prevent vaccine makers from relying on EMEA or FDA approval to register their vaccines elsewhere.

Prequalification may be the better option. The World Health Organization Prequalification Program "Appl[ies] unified standards of acceptable quality, safety and efficacy"⁶⁰ to medical products, working with experts and/or approved national drug regulatory authorities to select important medicines for use by the United Nations. Prequalification also opens the door to broader partnerships with humanitarian distributors.⁶¹ In addition, prequalification is a valued international symbol of quality, easing registration with most countries' regulatory agencies considerably. Prequalification could therefore

text accompanying note 65) (last visited Apr. 30, 2009). There may be other patents set to expire later, and there remains the possibility of patent "evergreening," filing new patents on the same products for relatively minor changes, which could extend the patents considerably longer. Absent licenses, Merck and GSK will be able to use patents to block competition until all patents covering technology necessary to produce HPV vaccines expire.

⁵⁸ Practically, even absent linkage, most generic vaccine makers might not apply for FDA approval so long as the originator products are patented. See Michelle Meadow, *Greater Access to Generic Drugs: New FDA Initiatives to Improve Drug Reviews and Reduce Legal Loopholes*, FDA CONSUMER, Sept.-Oct. 2003, at 14. But if there were a pathway to generic vaccine approval and no linkage, FDA approval would at least be technically possible as a strategy to assist worldwide registration, even if the U.S. market would not be available for sales.

⁵⁹ New products receive eight years of data exclusivity, after which follow-on companies may file "biosimilar" applications. Biosimilars will not be approved for sale until another two years have passed. See generally Janie Mackay, *bioLOGIC Europe 2007*, 10 IDRUGS 543 (2007). If the innovator also receives approval for new uses of the original product, this can add one additional year of data exclusivity, for a total of eleven years available exclusivity (8+2+1) following marketing approval. European Generic Med. Ass'n, Data Exclusivity, <http://www.egagenerics.com/gen-dataex.htm> (last visited Apr. 30, 2009).

⁶⁰ WHO, *supra* note 55.

⁶¹ *Id.* "The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Programme is used principally by United Nations agencies — including UNAIDS and UNICEF — to guide their procurement decisions. But, the list has become a vital tool for any agency or organization involved in bulk purchasing of medicines, be this at country level, or at international level, as demonstrated by the Global Fund to Fight AIDS, Tuberculosis and Malaria." *Id.*

be very important to rolling out a low-cost generic vaccine, particularly if timely approval by the FDA or other top agencies might not be possible.

Both Merck and GSK have applied for WHO prequalification of their HPV vaccines, suggesting HPV vaccines as a class may be candidates for prequalification.⁶² Several countries whose manufacturers have previously successfully prequalified vaccines,⁶³ including Brazil, India, and Cuba,⁶⁴ are subject to neither linkage nor data exclusivity. Their regulatory agencies might be able to provide a first step toward prequalification. Depending on the preparedness and efficiency of regulatory pathways and prequalification standards for a generic HPV vaccine at WHO, developing the data necessary for prequalification may be prohibitively expensive. Perhaps prequalification would require development of new WHO regulatory standards. But generic vaccines might be able to rely on some clinical data from Merck and GSK or otherwise, like the EMEA biosimilars pathway, engage in comparability exercises. And a number of vaccines, including those produced by developing countries,⁶⁵ are prequalified today. The WHO may also come under political pressure from brand-name companies and some wealthy countries for prequalifying a third (if WHO will have already prequalified Gardasil and Cervarix) generic (not truly generic, they will say) HPV vaccine. But if the generic vaccines are much less expensive than Gardasil and Cervarix, support for prequalification from the public health community will be strong. Prequalification therefore may be a viable option.

A second option would be to go through Europe, in spite of data exclusivity. The new European “biosimilars” pathway could keep data development and registration costs down. EMEA approved five biogenerics between 2004 and spring 2008 (although the authors are uncertain whether EMEA biogeneric standards would apply to generic HPV vaccines). Also, there is at least one path around data exclusivity: compulsory licensing for data. Though no country has yet issued such a license, the logic is much the same as compulsory licensing for patents,⁶⁶ and the Office of the United States Trade Representative has publicly stated countries would be within their rights to use it.⁶⁷ Governments and health advocates could seek compulsory

⁶² *Gardasil® Applies for WHO Certification to Reinforce Global Access to the Vaccine – Approval Would Qualify Gardasil® for Procurement by United*, MED. NEWS TODAY, Jul. 18, 2007, <http://www.medicalnewstoday.com/articles/77039.php> (Merck); *GSK Applies for WHO Prequalification of HPV Vaccine Cervarix*, MED. NEWS TODAY, Oct. 12, 2007, <http://www.medicalnewstoday.com/articles/85302.php> (GSK).

⁶³ “The [National Regulatory Authority] of the producing country is found to meet all the critical indicators defined for prequalification purposes following a WHO independent assessment.” WHO, PROCEDURES FOR ASSESSING THE ACCEPTABILITY OF VACCINES FOR PURCHASE BY UNITED NATIONS AGENCIES 3 (2006), available at www.path.org/vaccineresources/files/Procedures_acceptability_purchase_by_UN.pdf.

⁶⁴ The WHO prequalified vaccine list is available at WHO, WHO, List of Vaccines for Purchase by UN Agencies as of April 2009, http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html (last visited Apr. 14, 2009).

⁶⁵ *Id.*

⁶⁶ The authority to license data is also implicit in the authority to issue compulsory licenses for patents, for what good would such licenses be if data exclusivity prevented registering generics in any event?

⁶⁷ See Brook K. Baker, Presentation to Consumer Project on Technology - Next Steps and Strategies on Bilateral Free Trade Agreements, Using FTA Side Letters and Congressional

licenses for export, under WTO Paragraph 6-implementing legislation, on Merck and GSK vaccine data, to ensure data exclusivity does not delay registration of an important public health development around the globe (compulsory licenses for data could also be issued in vaccine-importing countries with data exclusivity). Europe would become one possible efficient source for quality assurance on which developing countries and perhaps WHO prequalification could rely.

Broader knowledge of country-by-country Global South registration requirements and WHO vaccine prequalification, beyond the scope of this paper, would help public health advocates plan a registration effort. Perhaps cost-effective HPV vaccines would be important enough that drug regulatory authorities would be willing to rely on a variety of reputable quality indicators in order to bring them to market. Regulatory approval in a major manufacturing country, even absent prequalification, might suffice – though all possible steps to assure vaccine quality should still be taken. Of course, data protection and linkage deterring generic HPV vaccines will eventually expire in all countries. Regulatory pathways may have improved by that time, and there will be more options available for vaccine makers to earn the approval of key regulatory agencies, easing global registration. But in that case, the patents having expired, compulsory licensing will no longer be a useful tool, and, moreover, many lives will have been lost to cervical cancer. As Kevin Outterson noted at this symposium's opening, when it comes to preventing HPV, time saved equals lives saved. If a low-cost, high quality generic vaccine can be made, it should, if possible, be registered by the major agencies or prequalified as soon as possible, so it can be efficiently registered and distributed everywhere.

C. IDENTIFYING HPV VACCINE PATENTS

So long as the HPV vaccines are patented in either the potential generic vaccine importing or vaccine exporting country, compulsory licenses will be necessary to authorize their use. The vaccines will probably be patented in major manufacturing countries, but determining this with certainty, and determining whether licenses for domestic use will be necessary in any given importing country, requires investigation.

Now of course, the simplest way to find out whether the vaccines are patented in a country is to ask. But surprisingly, in many developing countries, the patent office might not immediately know. Pharmaceutical companies do not ordinarily disclose which drugs they have patented in which countries, and they are not presently required to. Most governments, particularly in developing countries, have not yet developed patent databases linked to products' commercial names. And so, in many countries, learning whether a product is patented is not so simple as searching online or asking the government. As of this writing, we are not aware of a simple global public listing of all countries where the HPV vaccines are patented.⁶⁸ Vaccine-access advocates probably do, however, have the information and tools needed to

Letters to Authorize Waiver of Data Exclusivity and Linkage, (Nov. 16, 2006), *available at* www.cptech.org/events/BrookBakerFTA.ppt.

⁶⁸ There are, however, public databases listing patents for the wealthy countries.

build a near-comprehensive, if not quite complete, list, and to learn whether the vaccines are patented in a given country.

Although patents are public documents, patent claims typically do not state the commercial name, and sometimes do not state the international nonproprietary name (generic name), for a medical product, describing instead molecules or chemical compounds or methods of synthesizing compounds. This sometimes makes it hard to know what medical product a patent covers just by reading it, and, moreover, can make a relevant patent hard to find. Some countries, including the United States and Canada, list patents in databases⁶⁹ under the name of the medicine they cover.⁷⁰ Most countries have no equivalent publication. Pharmaceutical companies may be the only organizations that know which drugs they have patented. This is ironic, given part of the theory of patents is to award private market exclusivity in exchange for disclosure of new technologies to the public. In most countries, patents are technically disclosed, in that they are placed in public files. But they are not disclosed in ways that are always useful to citizens, or even to many government agencies, without investing significant time and effort. This makes it harder to plan health care policy.

Merck and GSK presumably maintain a listing of countries where they and their licensors (such as Australian researchers and HPV patent holders Ian Frazer and Jian Zhou) claim patents. But if public health officials are unable to access this information directly, there are other ways to build such a list, and learn, when the patent office does not immediately know, whether the vaccine is patented in a given country. Commercial databases provide patent information for a fee, but these often do not cover the small markets. Generics firms or NGOs may sometimes know, due to their prior work in a country.

If a patent office has compiled all patents in an electronic database, basic searches of a patent office's electronic files for non-proprietary drug names may reveal patents on key medicines or vaccines (and this is how many patent searches are conducted). But this is likely to leave out many patents that do not mention the medical product by name. Patent offices can conduct more

⁶⁹ The FDA's Orange Book is an example, though notably, it excludes the HPV patents. The Orange Book lists patents for drugs approved under the Food, Drug and Cosmetic Act; but Gardasil was approved under the Public Health Services Act, which regulates most biologic drugs and vaccines. The Electronic Orange Book, or Approved Drug Products with Therapeutic Equivalence Evaluations, is *available at* Food and Drug Administration, Electronic Orange Book, <http://www.fda.gov/cder/ob/> (last visited Apr. 14, 2009) [hereinafter Electronic Orange Book].

⁷⁰ In the United States, drug patent disclosure is a precondition of marketing approval. The Drug Price Competition and Patent Term Restoration Act of 1984 (more commonly known as the Hatch-Waxman Act) requires every person introducing a drug into commerce to file a new drug application (NDA) with the Food and Drug Administration (FDA). Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301, 355, 360cc (1994); Creation of Remedy, 28 U.S.C. § 2201 (1994); Issue of Patents, 35 U.S.C. §§ 156, 271, 282 (1994)). The NDA must include patent information—specifically, the patent numbers and expiration dates of patents that might reasonably be asserted in an infringement action. Drugs cannot be marketed until the FDA approves this application. *Id.* The FDA's Orange Book includes the submitted patent information in its Addendum, making it a little easier for generics manufacturers or health agencies to research patents held on critical medicines. Electronic Orange Book, *supra* note 69.

complete searches by using international patent listings as a guide. It is worthwhile, briefly, to mention the steps involved, so they can be used in future patent searches.

Health Canada (the Canadian health ministry) maintains an incomplete but useful online patent database at <http://www.patentregister.ca/> (so does the FDA, but as it turns out, the FDA's Orange Book does not list the HPV patents).⁷¹ A patent officer in any developing country could for instance look up Gardasil by its commercial name. The search will reveal both drug and patent information, including Gardasil's Canadian patent numbers 2113712 and 2215834. These numbers, in turn, can be entered into Europe's public databases to reveal the corresponding international patent number (priority number). The European Patent Office provides several portals to these databases at <http://www.epo.org/patents/patent-information/about.html>.⁷² Entering CA2113712 reveals international priority numbers AU1991PK07322 19910719 and WO1992AU00364 19920720; entering CA2215834 reveals priority numbers US19950408669 19950322; US19950409122 19950322; WO1996US03649 19960318.

The patent officer can use these numbers to search her own domestic database. Patents on file domestically should list the international priority numbers. If the priority numbers have been entered into the national patent database in a systematic way,⁷³ the patent officer should discover whether or not these patents are on file in her country.⁷⁴

⁷¹ *Id.*

⁷² For example, to access Great Britain's page, go to <http://www.epo.org/patents/patent-information/about.html>, click "Free databases," follow "esp@cenet," then "esp@cenet in your language," then, <http://gb.espacenet.com/search97cgi/s97.cgi.exe?Action=FormGen&Template=gb/EN/home.htm>. Choose "Number Search," and place the country abbreviation (in this case "CA" for Canada) before the numbers found on the Health Canada (or FDA, or other) website. Here, entering CA2215834 reveals a Merck patent; entering CA2113712 reveals a Frazer/Zhou patent.

⁷³ It will be easy to look up patents if every time an application is filed, a priority number of US19950423387 19950425 (corresponding to the HIV/AIDS medicine Kaletra) is entered in precisely that format. If, however, country codes, spaces and dashes are treated differently with each application - such that the same patent listed above could read "1995042338719950425" - or if the number is entered incorrectly, or if the numbers are not always entered into the database, or if the number sequences entered are pulled from different sources each time, such a search could become unreliable (note that a search for only part of the number sequence - for example, 19950423387 - should turn up results so long as the number was entered correctly in some form). *Id.* In such a case, the patent officer might have to employ one further creative method: reading the international patents for unique keywords that are likely to be listed in the national patent (some patent offices use this method). For example, U.S. or European patents might include specific terms describing a drug's chemical makeup that are distinguishable from other drugs to an informed reader. These terms could be entered into a national database as a keyword search. It may be helpful if someone with a background in chemistry or pharmaceuticals is available to assist.

⁷⁴ This does not necessarily mean the patents are valid, but assessment of the validity of the HPV patents is beyond the scope of this paper. For health policy planning purposes, the HPV patents sharing the aforementioned priority numbers have not been discredited.

Also recall some patents related to key medical products, such as those only covering the product when used in combination with a tangential product, may not create barriers to generic competition. That is, if a patent specifically protects *only the combination* of Medicine A and Medicine B, then it does not protect Medicine A used without Medicine B. Generics companies are free to market Medicine A unless a separate patent specifically protects Medicine A, its essential components, or exclusive manufacturing process. This point is

Some HPV vaccine patents on the books in a given country may not be valid. Patents held by prominent entities in the HPV vaccine field and patents recognized in multiple countries including major markets are probably more likely than others to withstand a challenge. Generic vaccines (and second-generation vaccines) using the same processes or components as the brand-name products would probably infringe valid patents, and would probably need licenses to authorize broad distribution. Patent holders might not launch infringement actions in some cases of humanitarian vaccine donation. But alleged patent-infringing vaccine distribution broad enough to offer economies of scale and meet need would probably encounter a legal challenge.

Second-generation vaccines that use different processes and components from the brand-name products might not infringe patents, and in this case, could be used without compulsory licenses. That is to say, some vaccine makers may be able to “design around” existing patents. But evaluating the substance of patents can be costly and risky. It seems likely second-generation vaccines may still rely on underlying first-generation technology, in which case the original patents could still block competition.

Hence, compulsory licenses are potentially necessary not only for generic vaccines, but also next-generation HPV vaccines. Where politically possible, it may be a good idea to issue compulsory licenses in either case, and remove any uncertainty from the patent landscape. Further, open compulsory licenses signal a secure market to generics firms, and can help attract investment and product registration.

D. UNDERSTANDING COMPULSORY LICENSING REGULATIONS

Many, but not all, countries now share the TRIPS Article 31 obligations. Countries also have domestic intellectual property laws, and some, such as Colombia,⁷⁵ may have detailed compulsory licensing regulations issued by administrative agencies such as the patent office or industrial property authority. Together with the TRIPS agreement, domestic laws and regulations spell out the procedures and conditions required to issue a compulsory license, and it is important to study them at the outset. National intellectual property laws are often available online through the World Intellectual Property Organization.⁷⁶ While requirements vary, there are patterns that

relevant because patents held by little known companies sometimes surface in patent searches, claiming use of a variety of established medicines in combination with a separate, lesser known product. These patents cannot control use of the established products except as used in conjunction with their own. In other words, not every patent naming a medicine somewhere in its text actually prohibits competition with that medicine.

⁷⁵ Regulations for compulsory licensing in Colombia are found in Superintendencia de Industria, Comercio y Turismo, Resolución No. 17585 (2001); Superintendencia de Industria, Comercio y Turismo, Decreto 4302 (2008).

⁷⁶ The World Intellectual Property Organization’s (WIPO) online portal is <http://www.wipo.int/portal/index.html.en>. Countries should generally consolidate their international obligations (TRIPS if already applicable, trade agreements, etc.) in the domestic law, but occasionally this might not happen. For example, Ecuador has its own Law on Intellectual Property (1998), with distinct terms, but also is a member of the Andean Community, which applies a Common Intellectual Property Regime (2000) for its members. Arguably, the two are not consistent (see, e.g., differences in the compulsory licensing chapters), but Ecuador has not amended its law to account for any differences. See Treaty Creating the Court of Justice of the Cartagena Agreement, art. 1, March 10, 1996

repeat across many countries. Some countries procedures are more onerous than others, but most will accommodate public health needs if appropriately framed.

Beyond the TRIPS guidelines, some common domestic law provisions specify the grounds on which a license may be granted – often, the broad “reasons of public interest” is an option, but sometimes grounds are limited to “emergency” or “national security.” In some cases, regulations or political forces will assign a particular agency to issue licenses, and sometimes a separate agency to determine whether an adequate public interest is at stake, or whether a given public health issue constitutes an emergency. These terms are broad, and there are rarely clear legal grounds to limit the cases in which a compulsory license may be issued. More often, it is a question of political will.⁷⁷

E. GENERATING PUBLIC AND KEY STAKEHOLDER SUPPORT

Two challenges vaccine access advocates are likely to encounter are a relative lack of knowledge of compulsory licensing on the part of government officials, and skepticism of compulsory licensing inspired by myths about its limitations. These myths, discussed in more detail in Section II, include the false notions that compulsory licensing is for emergencies only – which the WTO calls a “common misunderstanding”⁷⁸ (WTO rules in fact permit countries to determine the circumstances in which they will issue licenses), and that compulsory licenses can only be used to manufacture medicines domestically (in fact, TRIPS rules permit using compulsory licenses to import, and, with certain conditions met, export generic HPV vaccines).

There is, of course, also the expected opposition of Merck and GSK, and possibly the opposition of some wealthy governments, as well – although this may be a difficult case for them politically. Some observers suggest compulsory licenses are not an optimal solution to access problems because they come under political pressure. We respectfully disagree. In some cases, this pressure is a sign of the licenses’ efficacy. Though a relatively nascent tool for most countries (available or relevant since the TRIPS agreement entered

(discussing direct applicability of Andean Community decisions in member countries), *available at* http://www.comunidadandina.org/ingles/normativa/ande_trie2.htm. A non-official translation of Andean Community Decision 486: Common Intellectual Property Regime is available from the Andean Community at <http://www.comunidadandina.org/ingles/normativa/D486e.htm>. Ecuador’s Law on Intellectual Property can be accessed through the World Intellectual Property Organization Collection of Laws for Electronic Access portal. World Intellectual Property Organization, Collection of Laws for Electronic Access (CLEA), <http://www.wipo.int/clea/en/index.jsp> (accessed on May 25, 2009).

⁷⁷ In some cases, no clear procedures for issuing compulsory licenses are specified in the law. Government officers may be hesitant to initiate the licensing process without clear protocol guiding their decisions. For these reasons, it makes sense for governments to implement public health-friendly compulsory licensing regulations where they do not yet exist. The danger is implementing regulations that unnecessarily restrict government action. Regulations should ideally specify several possible clear paths to compulsory licenses, enabling anyone to request licenses and not limiting authority to grant them to any single government agency.

⁷⁸ See WTO, TRIPS and Public Health, *supra* note 32. Note that while some countries may restrict the grounds for issuing compulsory licenses to situations of emergency or national security, most do not, and WTO rules leave the grounds entirely open. *Id.*

into effect), a number have already used it effectively to promote access to medicines, and awareness of the tool's utility is growing. Each country that issues a compulsory license will make it politically easier for the next to do the same. If cost-effective generic HPV vaccines can successfully be produced, we believe demand for access to the vaccines through compulsory licensing will be strong enough to overcome political hurdles.

F. REQUESTING VOLUNTARY LICENSES

Government use licenses (those issued by a government to itself to supply public treatment or prevention programs, but not extending to private pharmacies) and licenses issued for emergencies generally may be issued at any time, without prior negotiations with the patent holder (some domestic laws may hold differently). In most other cases, prior negotiation is required by TRIPS.⁷⁹ Even in cases of government use, it may be advisable to request licenses from the patent holder before issuing compulsory ones. Voluntary license requests demonstrate respect for patent holders' interests and desire to come to a mutually acceptable compromise, and reduce the reasons to criticize any compulsory licenses that follow.

While negotiations with pharmaceutical companies usually focus on price discounts, TRIPS actually requires *license* negotiation⁸⁰ – in other words, requests to introduce generic competition. To comply with the requirement, governments or other entities would send such requests, in the form of letters including basic terms for the suggested licenses, to Merck and GSK. If the companies respond favorably, the country may enter into negotiations, perhaps yielding voluntary licenses permitting competition on the same grounds as compulsory licenses. If the company does not respond positively within “a reasonable period of time”⁸¹ – 90 days is certainly sufficient – countries are then free to issue compulsory licenses.

G. ISSUING COMPULSORY LICENSES

Countries prepared to issue compulsory licenses must resolve several final questions: to whom will they extend the license, at what royalty rate, and on what grounds.

Countries may grant licenses to specific actors or leave patents open to all qualified applicants (open licensing). For example, a license could be granted to the health ministry to allow it to purchase generic vaccines, or to a firm to manufacture or import a vaccine. In the case of an open license, any party can make use of the patented invention, provided they comply with terms specified by the patent office (such as meeting national drug quality standards and paying the required royalties).

The authors strongly recommend the use of open licenses. Open licenses allow more firms to enter the market, permitting the country to gain the benefits of broader competition. Open licenses also save countries the trouble

⁷⁹ TRIPS, *supra* note 23, art. 31(b). Licenses issued to remedy anticompetitive practices are another exception. *See id.* at art. 31(k).

⁸⁰ *Id.*

⁸¹ *Id.*

of selecting particular providers of a vaccine, should there be more than one. This also avoids the need to issue subsequent licenses if the designated producer leaves the market or fails to meet demand for any reason.

Countries also have the option to limit licenses to public, non-commercial use (also known as government use). This allows the government to manufacture generics itself or to acquire generics from private firms for purposes of supplying public programs. But government use licenses do not allow generics firms to sell their drugs or vaccines in private pharmacies or otherwise on the private market. Government use licenses offer the advantage of exempting countries from prior negotiation requirements under TRIPS. Hence, they allow countries to issue compulsory licenses immediately, without waiting “a reasonable period” for a reply from pharmaceutical companies. But they prevent generics from competing with patented medicines on the private market. In the case of the HPV vaccine, government use licenses are a possibility, as the objective will presumably be a broad public vaccination campaign. If, however, a country plans to rely on private market purchases to round out vaccination, it may wish to not limit licenses to government use.

National, regional and international intellectual property rules require that a compulsory license licensee must pay compensation to the patent holder. TRIPS Article 31(h) requires that a licensee must pay “adequate remuneration” to the patent holder, “taking into account the economic value of the license.” In recent years, a number of developing countries have issued compulsory licenses on HIV/AIDS drugs. Malaysia set a royalty rate of 4 percent for such licenses; Mozambique established a 2 percent royalty; Zambia set a 2.5 percent royalty; and Indonesia arrived at 0.5 percent royalty. Thailand established a 0.5 percent royalty on the AIDS and heart disease medications it compulsorily licensed.

Several governments and international agencies have established or proposed pharmaceutical licensing royalty systems in recent years. A UNDP proposed set of guidelines suggested royalties from 0 to 6 percent of the price charged by the generic competitor. The 2005 Canadian royalty guidelines for the export of medicines to countries that lack manufacturing capacity set royalties at 0 to 4 percent of the generic price, depending upon the level of development of the importing country.

In the pharmaceutical industry, voluntary license rates range widely, but seem generally to be in the four to five percent range. The leading publication on royalty rates in compulsory licensing cases is the joint UN Development Program-World Health Organization publication “Remuneration Guidelines for Non-Voluntary Use of a Patent on Medical Technologies.” It notes:

There is extensive experience of voluntary technology licensing in the private sector. The evidence of compensation for private, market-based license arrangements provides an important context for making determinations of royalty and remuneration arrangements in cases of compulsory licensing. There is some conflicting evidence on cross-industry licensing averages, but there seems to be agreement in reports from the pharmaceutical industry and others that licensing fees for the pharmaceutical industry congregate at 4-5%. The pharmaceutical industry has one of the higher licensing rates among all industries.⁸²

In one notable and relevant case, Gilead has provided voluntary licenses to eight Indian generics firms to produce two important AIDS drugs for sale in 95 countries. The royalty rate in this agreement is set at five percent.

We recommend in general that countries issuing compulsory licenses not seek to reduce royalty rates to the lowest possible levels. A somewhat higher rate applied to a low-cost generic product has a relatively small effect on the wholesale or retail price of the drug, provides assurances that patent holders are being treated fairly, and signals that the government issuing the license is committed to making reasonable contributions for the innovation embedded in the product.

The mechanism for issuing compulsory licenses varies. Some countries require a declaration of public interest, emergency or national security. Public interest grounds are the best of these options. Promoting affordable medicines clearly promotes the public interest, and a declaration of public interest does not create unnecessary concerns about conditions in a country or invite debate as to whether a particular public health problem qualifies as an emergency.

Declarations granting compulsory licenses can be simple and brief. In Brazil, the Minister of Health declared efavirenz to be of public interest one week before issuing a joint declaration with President Lula granting the actual license. But this can ordinarily be accomplished in one step. HPV vaccine licenses should grant licensees rights to use any patents necessary, held by any of the HPV patent holders, to develop, manufacture, offer for sale, sell, import (in Paragraph 6 cases, export) or use HPV vaccines, to avoid any problems regarding access to the overlapping rights held by Merck, GSK and the Australian researchers.

H. LICENSING IN MULTIPLE COUNTRIES

Because patents are issued on a country-by-country basis, compulsory licenses must also be issued country-by-country. This does not prevent health advocates from approaching HPV vaccine patent licensing as a global effort. Global license requests can be made of Merck and GSK, and as widespread compulsory licensing appears more likely, they may become more likely to negotiate. Governments and civic groups can pool resources to identify

⁸² JAMES LOVE, HEALTH ECONOMICS AND DRUGS, TCM SERIES No. 18, REMUNERATION GUIDELINES FOR NON-VOLUNTARY USE OF A PATENT ON MEDICAL TECHNOLOGIES, 6 (2005), available at http://www.who.int/medicines/areas/technical_cooperation/WHOTCM2005.1_OMS.pdf. For a more extended discussion, see *id.*, at 45-49.

patents and build a global patent list, to help bring generics to market, assist registration, and build public support for licenses. Indeed, as more markets open to generic vaccines, financial incentives for generics firms will grow, and if they succeed in bringing vaccines to market, they will gain economies-of-scale benefits that could bring prices of HPV vaccines, and other products, down considerably in the future.

I. FOLLOWING UP

Countries are free to begin manufacturing and importing generic vaccines once compulsory licenses have been issued. This does not mean that generics will necessarily be automatically forthcoming. Health ministries may still need to search the international market for providers and help them traverse the obstacles to registration noted above. Governments and health advocates should pay lasting attention to their efforts to provide the licensed vaccines to the public and make sure they are successful.

V. CONCLUSION

Compulsory licensing is an essential tool in the access to medical technology toolkit. Like many tools, it is appropriate only for certain tasks. In the case of the HPV vaccine, compulsory licensing will be useful:

- 1) If high-quality generic HPV vaccines can be produced and transported at low-cost, be broadly and efficiently registered, and priced below Gardasil and Cervarix;
- 2) Where the Merck and GSK products are patented, if the companies are unwilling to grant licenses on a voluntary basis, and, in the case of exporting patented vaccines, if the manufacturing country has implemented WTO TRIPS Paragraph 6 legislation.

The HPV vaccines probably are patented in manufacturer countries, and sufficiently competitive voluntary license arrangements for medical products are uncommon. Thus, if generic (or second-generation) vaccines can be developed and registered in the near future – before patent protection expires – compulsory licensing will probably be a critical component of a global vaccine access strategy, playing a pivotal role in ensuring vaccinations against HPV are available to all, around the world, regardless of ability to pay.

Some of the barriers outlined in previous pages could pose formidable – and perhaps insurmountable – hurdles to the successful use of compulsory licensing of this particular product in the near term. Of particular concern are the possible scientific and regulatory challenges to manufacturing and registering generic HPV vaccines, and the likelihood manufacturing would in any event be concentrated in very few countries. It will help if more manufacturing countries adopt Paragraph 6 legislation, enabling them to export vaccines under compulsory license.

If barriers to making low-cost generic HPV vaccines prove insurmountable in the near term, the analysis provided in this paper can still assist governments, humanitarian organizations and others to evaluate the appropriateness of compulsory licensing as a tool to promote access to other

life-saving products. For many products, the hurdles will not be so great. Important examples include the prohibitively expensive newer, second-generation drugs for HIV-AIDS, as well as other traditional, chemical-based drugs aimed at additional diseases, which will not face the manufacturing and registration hurdles unique to biologic products like the HPV vaccine. The context for every product will necessarily be different. But as brand-name companies intensify global patenting, compulsory licensing as a tool to promote access to affordable medical technology becomes ever more important.