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Intellectual property rights and challenges for development of affordable human papillomavirus, rotavirus and pneumococcal vaccines: Patent landscaping and perspectives of developing country vaccine manufacturers

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ABSTRACT

The success of Gavi, the Vaccine Alliance depends on the vaccine markets providing appropriate, affordable vaccines at sufficient and reliable quantities. Gavi's current supplier base for new and underutilized vaccines, such as the human papillomavirus (HPV), rotavirus, and the pneumococcal conjugate vaccine is very small. There is growing concern that following globalization of laws on intellectual property rights (IPRs) through trade agreements, IPRs are impeding new manufacturers from entering the market with competing vaccines. This article examines the extent to which IPRs, specifically patents, can create such obstacles, in particular for developing country vaccine manufacturers (DCVMs). Through building patent landscapes in Brazil, China, and India and interviews with manufacturers and experts in the field, we found intense patenting activity for the HPV and pneumococcal vaccines that could potentially delay the entry of new manufacturers. Increased transparency around patenting of vaccine technologies, stricter patentability criteria suited for local development needs and strengthening of IPRs management capabilities where relevant, may help reduce impediments to market entry for new manufacturers and ensure a competitive supplier base for quality vaccines at sustainably low prices.

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1. Introduction

Established in 2000, Gavi is a public private partnership that facilitates access to lifesaving vaccines for low-income countries, using an innovative model to pool donor funds and support country immunization priorities. From inception to December 2013, Gavi had invested US$8.7 billion in over 70 countries, helping to prevent over six million future deaths through immunization. Gavi's success depends on the vaccine markets providing appropriate, affordable vaccines at sufficient and reliable quantities. "Shaping vaccine markets" is therefore, one of four strategic goals in the Gavi Alliance strategy 2011–2015 [1]. The aim is to ensure an adequate supply of quality vaccines that meet demand at low and sustainable prices. Through targeted interventions and strategic procurement, Gavi tries to encourage new vaccine manufacturers to enter the market as a means to increase competition, thereby increasing supply and putting a downward pressure on prices [2].

The current supplier base for many of the new vaccines purchased by Gavi is very small, but progress has been made in some product markets: in 2001, Gavi began to procure pentavalent vaccines—which combine the antigens for five infectious diseases in a single shot—from just one manufacturer [3]. By 2014, this has increased to six manufacturers, two of which are based in India. While historically, manufacturers based in the United States and Europe have dominated most vaccine markets, development and manufacturing capacity has increased in other parts of the world over the last two decades [2]. Nevertheless, no developing country manufacturers have yet brought follow-on versions of newer

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vaccines, such as the human papillomavirus (HPV), rotavirus, and pneumococcal conjugate vaccines to market [3–5].

Simultaneously, international trade agreements require countries with vaccine manufacturing capabilities to provide patent protection for pharmaceutical and biological products under the WTO agreement on trade-related aspects of intellectual property (TRIPS). This article summarizes the results of a study funded by Gavi, which explored whether patents and other intellectual property rights (IPRs) act as barriers to new manufacturers and especially developing country vaccine manufacturers (DCVMs), particularly for the HPV, rotavirus, and pneumococcal conjugate vaccines. The objectives of the study were to (1) identify documented and potential effects, if any, of IPRs (in particular patents) on access to essential vaccine technologies that enable manufacturers to develop new vaccines; (2) identify perceived barriers that may deter or delay market entry of manufacturers.

2. Methods

The study used three approaches: (1) literature surveys to identify potential barriers that IPRs may create for research, development, and commercialization of novel vaccines and/or combinations of existing vaccines by competitive suppliers. This included a review of peer-reviewed papers, and policy documents relevant to vaccine development and intellectual property. Researchers evaluated existing mechanisms to promote vaccine development and purchasing of vaccines for Gavi eligible countries through the reduction of IPRs barriers, including the TRIPS flexibilities (See Supplementary Data for details of literature review).

(2) Case studies to assess and analyze the impact of IPRs on the development of HPV, rotavirus, and pneumococcal conjugate vaccines. These vaccines were chosen because they are relatively new and have been prioritized for Gavi funding. They also have been cited as having complex IP landscapes [6]. The research included unstructured interviews with expert informants, such as researchers, technology transfer professionals, representatives of public health agencies, and developing country vaccine manufacturers (See Supplementary Data for details of methods used for interview study and qualitative analysis). To build a patent landscape, a search was made for US patents or international patent applications (PCT) using keywords in the description and claims of patent documents. Given the various technologies that go into manufacturing a vaccine, the keywords used were deliberately broad in order to capture as many relevant patents as possible. Inventor and names were also used to build upon key word searches. Additional searches used names of companies currently marketing these vaccines as "assignee/applicant". Patent searches were focused on three countries, India, Brazil and China, with established vaccine manufacturing capacity from which Gavi already procures or plans to procure vaccines and in which manufacturers are known to work on the development of one or more of the three vaccines reviewed in the case studies. Patent data are current as of June 30 2012 (See Supplementary Data for details of methods used for building patent landscapes). WIPO recently released a report with patent landscapes of vaccines, which included the pneumococcal vaccines but not HPV and rotavirus vaccines [7]. The WIPO analysis was conducted at the same time as our study and while we identified a similar number of Patent Cooperation Treaty (PCT) applications as the WIPO report, some differences were observed between the PCV landscapes as a result of different searching strategies.

(3) An analysis of the landscape of stakeholders and policy proposals for reducing IPR barriers to facilitate development of new and underutilized vaccines. This included literature reviews and interviews with expert informants representing important stakeholder groups to solicit views on needs related to IPR management and potential solutions.

3. Results

3.1. Human papillomavirus vaccine

We identified 93 patents filed in the US or as PCT applications that would be relevant to the manufacturing of HPV vaccines. Of these the largest number of applications (43) has been filed in China. China also has the highest number of granted patents (16). Brazil has only granted one patent to date out of 31 filed. India has granted 13 out of the 30 applications filed (Fig. 1). Not surprisingly, the two companies with licensed HPV vaccines, GlaxoSmithKline (GSK) and Merck, dominate the patenting activity for HPV vaccine technologies in Brazil, China, and India (Supplementary Table 1–3).

Although the patent landscape for HPV vaccines is quite complex, the analysis suggests patents should not completely block new manufacturers from producing biosimilar vaccines based on major virus capsid protein L1 virus like particles (VLPs) equivalent to Cervarix and Gardasil or second-generation vaccines based on L2 capsid protein VLPs. However, given the number of patents identified and the subjective nature of claims interpretation, new manufacturers and in particular DCVMs do face uncertainty in navigating these patents, which could increase transaction costs and/or delay end products coming to market. Working around some key patents may also add costs and time to the development process.

For example, representatives of one Indian manufacturer stated that while their in-house preliminary FTO analysis suggested there was freedom to operate for developing an LI VLP-based bivalent or quadrivalent vaccine in India, patents filed by GSK separately claim a "Two dose regimen" for compositions containing HPV 16 and 18 VLPs and "providing cross-protection against other oncogenic HPV strains" such as HPV 31, 33, 45, 52, and 58 [8]. The manufacturer indicated that the scope of these patent claims is unclear and the patent status, particularly in other developing countries, are not fully known. Protection against HPV 33, 45, 52, and 58 is especially relevant to vaccines made for developing countries as epidemiological studies show these strains are highly prevalent in parts of Asia and Africa [9].

3.2. Rotavirus vaccine

We identified 29 patents filed in the US or as PCT applications that may be relevant to the manufacturing of rotavirus vaccines. GSK, the manufacturer of the vaccine Rotarix, has the most number of patents filed across the three countries. Merck, the manufacturer of Rotateq, does not appear to have any patents granted in Brazil, China, or India (Supplementary Table 1–3). Our landscape includes patents on technology underlying the bovine reassortant rotavirus vaccine (BRV) owned by the United States National Institutes of Health (NIH). This patent has been refused in Brazil, but is under appeal, and has been granted in China and India where it has been licensed to a number of developing country vaccine manufactures (DCVMs). SII and Bharat Biotech have filed applications for their vaccine candidates as well.

Based on analysis of the patent landscape, there do not appear to be any patent related barriers in Brazil, China, or India that would prevent the production of a BRV. However, new manufacturers seeking to make follow on versions of GSK's Rotarix vaccine may have to work around some of these patents depending on which markets they plan to sell their vaccines in. Representatives of WHO [10] also highlighted that patents on a liquid formulation for a rotavirus vaccine could be an impediment. Merck has broad patent claims on a liquid formulation of BRV, which have been

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