

Access to vaccine technologies in developing countries: Brazil and India[☆]

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Received 21 June 2007; received in revised form 31 August 2007; accepted 3 September 2007
Available online 20 September 2007

Abstract

This study, conducted by visits, interviews, and literature search, analyzes how vaccine manufacturers in Brazil and India access technologies for innovative vaccines: through collaborations with academia and research institutions, technology transfer agreements with multinational corporations, public sector, or developing country organizations, or by importation and finishing of bulk products. Each has advantages and disadvantages in terms of speed, market, and ability to independently produce the product. Most manufacturers visited are very concerned about avoiding patent infringement, which might result in undeveloped or delayed products because of a lack of mastery of the patent landscape. Disregarding the patent picture could also threaten the market of a potential product. Although it is too soon to assess the effects of TRIPS on vaccine technology access in Brazil and India, a good understanding of intellectual property management will be useful. A case study on development of a new combination vaccine illustrates these findings.

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Keywords: Vaccine innovation; Intellectual property rights; Technology transfer

1. Introduction

The role of emerging suppliers in supplying the international vaccine market has been growing in the past few years, not only in terms of volume, but also reflecting the range of products supplied. A primary issue is the mechanism by which these manufacturers access technologies for new vaccines, including how they manage intellectual property rights (IPRs). As part of its mandate, the World Health Organization

(WHO) is monitoring the impact of IPRs on access to priority vaccines for the developing world [1]. Earlier reports [2,3] showed little impact on access to traditional vaccine technologies, but because (1) emerging manufacturers are moving from *incremental* innovation (e.g. scaling up production using known processes) to *development* of new products; (2) stronger intellectual property laws have been adopted in developing countries in compliance with the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS); and (3) the domain of patentability is growing concomitant with an exploding number of patents, it was important to reassess the situation. This report describes the observations and implications of these issues in a study examining various methods of vaccine innovation, and the impact of TRIPS-compliance laws in India and Brazil, two countries where vaccine manufacturers are projected to be important sources of innovative vaccines for the developing world.

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1.1. TRIPS agreement

Under the terms of TRIPS, signed in 1995, all members of the World Trade Organization (WTO) have agreed to implement minimum standards for the protection of intellectual property. For pharmaceuticals, the most important provisions of the TRIPS agreement concerned the minimum length of protection (20 years from application) and patentable subject matter. All members of the WTO have to provide patent protection for pharmaceuticals, whereas several important developing countries like India previously refused to grant pharmaceutical product patents.² The TRIPS agreement included a number of provisions which have become known as TRIPS flexibilities. A *compulsory license* is an authorization granted by the government to a third party to practice the invention without the consent of the patent owner. The use of compulsory licenses is permitted under TRIPS, subject to a number of conditions. Countries can also choose to allow *parallel imports* by adopting an international exhaustion of regime. Under this regime, products can be imported without the consent of the patent owner, provided that the product was lawfully bought in the exporting country. Implementation of the TRIPS agreement was subject to different deadlines. The most important of these was 1 January 2005, by which time developing countries (except the least developed ones) that did not grant patent protection for pharmaceutical products had to do so. In effect, all developing countries³ with significant capabilities for the production of new vaccines for export have now implemented (or are now complying with) the TRIPS agreement. This implies that patent laws are to a large extent harmonized across these developing countries and developed countries. However, the patent situation for a particular product may be different in different countries since patents rights are granted at the national level.⁴

There has been widespread concern that implementation of the TRIPS agreement could have a negative impact on access to pharmaceuticals in developing countries. It was feared that the new patent regime would prevent developing countries from producing and/or importing new pharmaceuticals at low prices. Many academic papers and several important reports [4–6, and references therein] have been written on this issue. As the debate on TRIPS and access to pharmaceuticals has focused almost exclusively on drugs and in particular antiretrovirals, it is worth pointing out some

differences between vaccines and drugs and their implications.

Since vaccines are biological products administered to healthy subjects, their production and distribution is tightly controlled to ensure their quality and safety. Another distinguishing feature of vaccines is that their production requires a considerable amount of know-how that is not communicated by patents, and is costly and time consuming to acquire.⁵ As a consequence, the flexibilities in the TRIPS agreement such as allowing for parallel imports, the possibility to grant compulsory licenses, or protection of clinical trial data are unlikely to be relevant. Compulsory licensing does not provide the licensee with access to manufacturing know-how; thus, it is unlikely to be generally effective for vaccines, unless the know-how is readily available. Compulsory licensing of reverse genetics IP rights⁶ could be relevant for the production of pandemic influenza vaccines. In addition, because there is no bioequivalence procedure for vaccines, there is no such thing as a generic vaccine. Each product has to undergo at least limited clinical trials unless there is a strong correlate of protection and certainly for new production sites (influenza vaccines being a special case).

1.2. Developing country vaccine manufacture

The impact of vaccine production in developing countries on global vaccine supply has followed four different phases: early local production, maturation, technological expansion, and innovation. Each of these is characterized by different products, markets, and regulatory considerations.

1.2.1. Early local production

When the Expanded Programme on Immunization (EPI) was initiated in 1974, the vaccines included were Bacille Calmette-Guerin (BCG), diphtheria–tetanus–pertussis (DTP), tetanus toxoid (TT), measles, and oral poliovirus vaccine (OPV). Many countries, including developing countries, had initiated vaccine production in public sector facilities, especially for BCG and TT, but sometimes including other products characterized by traditional and widely available technology. In fact, many of the production methods were decades old.

1.2.2. Maturation

Despite widespread vaccine production, many countries had no reliable vaccine source. Accordingly, UNICEF Supply Division and the PAHO Revolving Fund⁷ began to buy

² Patent claims can be one of two types: they can cover a product – something that has a physical reality such as a machine or a substance – or a process (typically a method of production). Product patent protection is more desirable from the patent applicant perspective because infringement is easier to detect. In addition it is usually easier for third parties to invent around a process patent than a product patent.

³ Brazil, China, Cuba, India, Indonesia.

⁴ For instance, an Indian manufacturer may be prevented from selling in the United States by a US patent while having freedom to operate in India. This would be the case if (among other possibilities) no corresponding patent had been applied for in India.

⁵ Indeed, access to know-how is an important motivation for emerging manufacturer to enter technology transfer agreement, *vide infra*.

⁶ Reverse genetics is a method to produce vaccine seed by starting with the final product and recultivating it. Reverse genetics is an important technology in the context of pandemic influenza preparedness and is covered by several patents.

⁷ The Pan American Health Organization (PAHO) Revolving Fund and UNICEF are the two largest procurers of vaccines for public sector immunization programs.

these vaccines on behalf of developing countries. To do so, they tendered from known manufacturers, mostly in the US, Europe, and Japan, awarding tenders on the basis of price. To insure the quality, WHO was asked to advise, and the first procedure for this, referred to as prequalification, was defined in 1987 [7]. The UNICEF/PAHO tenders, requiring as they do prequalification of the products and oversight by a functional national regulatory authority (NRA) in the country of manufacture, provided a “gold seal of approval” for products. Regulatory requirements and manufacturing requirements, however, continued to evolve, making achieving prequalified status more difficult.

Most of the manufacturers supplying vaccines were large-scale European manufacturers who were able to provide products at advantageous pricing because of economies of scale and unused capacity. A few manufacturers from Warsaw Pact countries supplied products through a special distribution arrangement, and one developing country supplier, the Institut Pasteur Dakar, Senegal, was included, supplying first BCG and later yellow fever vaccines. In the mid-1990s, a second developing country supplier, the Serum Institute of India Ltd., and eventually a third, PT Bio Farma (Persero), from Indonesia, joined the group of suppliers, but these were definitely in the minority.

Many developing country manufacturers who supplied only their local immunization programs were unable to meet the WHO and UNICEF standards for procurement; thus, several of these manufacturers have ceased production. The decline of national public sector vaccine production and the increasing success of the EPI led to the enhanced role of manufacturers selling to UN agencies for the developing world vaccine supply.

1.2.3. Technological expansion

In 1992, the WHO proposed the addition of a seventh antigen, hepatitis B vaccine, to immunization programs worldwide [8], the first new antigen to be added for global use since the program began.⁸ It was revolutionary in another sense, in that most hepatitis B vaccines were made by recombinant DNA technology. It was thought at the time that recombinant technology was too complex to be used in vaccine production by developing country manufacturers. However, by 1999, two Korean manufacturers⁹ had recombinant hepatitis B vaccines on the global market ([2]; see also Ref. [3] for a detailed discussion of this case). This achievement was soon followed by additional hepatitis B vaccines from manufacturers in India and Cuba being added to the WHO-prequalified list.¹⁰

⁸ Yellow fever vaccine had also been added, but only for countries at risk.

⁹ Although the Republic of Korea is a large economy, at the time its manufacturers were not considered as industrialized country manufacturers. In fact, Korea's NRA is a member of WHO's Developing Countries Vaccine Regulators Network.

¹⁰ http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html, accessed 19 September 2007.

However, as more new vaccines were introduced into industrialized countries (originally vaccines such as *Haemophilus influenzae* type b – Hib, acellular pertussis, inactivated poliovirus vaccine – IPV, and measles–mumps–rubella, but now including vaccines such as those against rotavirus, varicella zoster, and human papilloma virus), the divergence between products used in public health programs in industrialized countries and those used in developing countries became an issue. Industrialized countries had traditionally supplied the same product at low price for developing countries and higher prices in developed countries. The potential for these differentiated prices became limited when the high end of the market was getting a different presentation (for example, a single dose, without thimerosal) or a different product entirely (such as IPV instead of OPV). Industrialized country manufacturers began to leave the global public market in favor of markets with higher return on their investment. This opened the way for more developing country suppliers to enter, supplying the traditional vaccines. In fact, if these suppliers had not been able to provide high quality products to the developing world, the prices paid for traditional vaccines would have greatly increased.

Perhaps the most important single factor in technological expansion as it impacted developing country manufacturers, however, was the emergence of the GAVI Alliance¹¹ with large amounts of funding available for vaccine purchase and an aim to ensure the introduction of new vaccines against priority diseases into even the poorest of developing countries. One of GAVI's priority antigens was Hib, ideally in a combination product. At the time this decision was taken, there were no combination products (including DTP–Hep B, DTP–Hib, and DTP–Hep B–Hib) manufactured by developing country manufacturers. But with the availability of funds to finance these products, combination products went to the top of the product development priority list for several of these manufacturers.

1.2.4. Innovation

Besides the increased amount of money in the global public vaccine market, manufacturers recognized the importance of a strong R&D pipeline, competence in process development, and the ability to access new technologies, as well as the need for recognized regulatory oversight. This situation has set the stage for what promises to be a huge change in vaccine supply during the early decades of the 21st century.

2. Methodology

Because India and Brazil had several vaccine producers, of which some had WHO-prequalified products, we selected these two countries for this study on technology access and

¹¹ The Global Alliance for Vaccines and Immunization and its Fund, collectively known as the GAVI Alliance, is a partnership focused on immunization initiated in 2000.

the impact of TRIPS. Most of the material for this paper comes from two field studies conducted in India in October 2005 and in Brazil in November 2006. The field studies consisted of on-site interviews with seven different vaccine manufacturers plus visits to the national patent offices. The general purpose of the field studies was to identify emerging vaccine producers' problems, capacities and needs in the field of intellectual property and intellectual property management and other aspects of accessing technologies. Assessing the effects of the new TRIPS-compliant patent laws adopted in these countries on the development of innovative vaccines was of particular interest, as were agreements for transfer of technology.

The preparation of the field studies benefited from prior work by WHO in this area and from access to unpublished firm-level data and findings from a prior study on emerging vaccine manufacturers [9]. An extensive literature search was conducted and additional information was obtained through publicly available patent databases. We also used information on technology transfer agreement available through the website of the Brazilian patent office (INPI).¹²

3. Results

3.1. Characteristics of producers and countries visited

3.1.1. Brazil

The two main Brazilian vaccine producers, Bio-Manguinhos¹³ and Instituto Butantan, share a similar mission. They are public entities with public health goals focused primarily on the Brazilian market. The Brazilian national immunization program is strong and this, combined with the large number of new infants born each year (3.7 million in 2005), generates substantial demand for vaccines. Butantan and Bio-Manguinhos enjoy a *de facto* monopoly on the large Brazilian public market; however, the prices are set by the Ministry of Health (MOH), and track the prices charged for similar vaccines by the PAHO Revolving Fund or UNICEF.

The relationship between the two public sector producers is complicated. There is little overlap between their product portfolio and under a non-competition agreement signed in 2002, if one is producing or developing a product, the other should not embark on a development project for the same product.

Brazil introduced a new patent law in 1996 (taking effect in 1997) in compliance with the TRIPS agreement. Brazil went further than the minimum TRIPS requirements by not making full use of the transition period, by offering pipeline

protection and by adopting national exhaustion of rights (which excludes parallel imports) [10]. There is a huge backlog in processing patent applications, which is particularly pronounced in the biological and pharmaceutical sector. As of November 2006, patent applications from 1997 to 1998 were being examined; in other technological fields, patents from 1999 to 2000 were being examined. Part of the more important backlog in the biological and pharmaceutical sector probably comes from the 'prior consent' practice, which is a unique feature of the Brazilian patent system. Under the 1999 law creating the drug regulation agency (ANVISA), both the patent office and the drug regulation agency examine pharmaceutical patent applications [11]. Despite the fact that ANVISA uses the same criteria (novelty, inventive step, industrial application) in patent examination as the patent office, they often reach different conclusions, which slows down the process.

As of November 2006, 120 new patent examiners were being trained, a substantial increase, given that total INPI staff numbered around 300. The pipeline is transparent, as applications are published 18 months after the priority date or the application date, whichever is earlier.

3.1.2. India

In India, we looked only at private sector producers, as there is little innovation among public sector manufacturers. However, public sector institutions like the Indian Council for Medical Research (ICMR) are accessing innovative technologies, such as for rotavirus and human papilloma virus vaccines, and making them available to manufacturers. While Indian vaccine manufacturers are increasingly sophisticated about managing innovation, they feel challenged in their ability to interpret patent claims or to challenge dubious ones. Thus, they will dedicate more time and resources to "invent around" the patent rather than risking infringement, that is, to avoid the use of the specific technology or avoid production of the product altogether.

India delayed implementation of the TRIPS agreement until the last possible moment, finally passing an executive ordinance on 26 December 2004. The ordinance was later replaced by the Patents (Amendment) Act 2005 which has retroactive effect from January 2005. The main change brought by the new patent law was the availability of product patent protection for all fields of technology. Previously only process patents were granted for pharmaceuticals. The delayed application meant that under the terms of the TRIPS agreement India had to put in place a transitional mechanism ("the mailbox") where applicants could file patent applications. These mailbox applications are to be examined under the new law passed in 2005 using the date of filing into the mailbox as the priority date. Slightly fewer than nine thousand of these 'mailbox' applications have been filed.

India's patent law contains some unusual features. One of them is that India uses an international exhaustion of rights regime, allowing parallel importations provided that the product was lawfully bought in the exporting country. Another

¹² Brazilian institutions are required by law to report the technology transfer agreements they enter to the Brazilian patent office (INPI).

¹³ Bio-Manguinhos is a part of the Oswaldo Cruz Foundation, or FIOCRUZ, which oversees issues related to patents and technology transfer agreements on behalf of Bio-Manguinhos.

is that new uses for known substances are excluded from patentability unless the new use results in improved efficacy (which might be interpreted to exclude patenting, for example of combination vaccines). The law has procedures for opposition both pre- and post-grant, as well as a revocation procedure, thus offering multiple opportunities for third parties to attack weak patents. These provisions, combined with the patent office's "well-entrenched history of adopting a conservative approach towards patentability" [12], are important for high patent quality.

The Indian intellectual property and legal systems are perceived by some manufacturers as lacking efficiency in terms of enforcement and hence unable to protect their interests to the fullest extent. In practice, access to patent documents is costly and difficult, rendering the pipeline of new patents less than transparent.

3.2. Innovation and pipeline

All manufacturers visited had innovative products in the pipeline, although most were developing existing products as well, and many projects were only improvements of existing technology. A mean of 28% (14–44%, depending on the manufacturer) of new antigens were being developed either by in-house research activities or by technology transfer. The summaries that follow are a static picture of a rapidly changing industry.

3.2.1. Brazil

In recent years there has been a significant increase in both R&D activity and expenditures in this area by Bio-Manguinhos. R&D activities are mostly funded from their own budget but some funds come from the Ministry of Health and from the Ministry of Science and Technology. Bio-Manguinhos has many collaborative activities with different universities. They have more than 15 vaccine R&D projects, including one on a dengue vaccine and one in collaboration with the Hookworm Vaccine Initiative, through their parent organization, FIOCRUZ. With technology transfer from Glaxo SmithKline (GSK) for Hib, and using DTP from Butantan, they have already developed a DTP–Hib vaccine and are now working on a pentavalent product which will include hepatitis B vaccine from Butantan. They have several agreements with GSK for bulk filling as well as transfer of technology (OPV, measles–mumps–rubella, Hib).

R&D spending has also increased at Butantan, financed by research grants, mainly from Sao Paulo's state science and technology support agency. A number of new R&D projects have been started, as follows: (1) Hib (said to be for export only); (2) hookworm vaccine (in collaboration with FIOCRUZ: Butantan will produce the antigens for the vaccine to be formulated at FIOCRUZ); (3) a combination rabies leishmania vaccine; (4) dengue vaccine (Butantan has obtained a non-exclusive license from the NIH to evaluate the technology); (5) HPV (loose agreement with University of Colorado); (6) rotavirus through a clone licensed from NIH

for vaccine development; (7) cellular pneumococcal vaccines (in collaboration with Children's Hospital at Harvard Medical School). They were expecting the rotavirus, dengue, pneumococcal cellular and the rabies–leishmania combination products to enter clinical trials in 2008. They are completing a technology transfer arrangement with Pasteur-Merieux (now Sanofi Pasteur) for influenza vaccine, which started with importation of bulk vaccine but will eventually be their own production.

3.2.2. India

Bharat Biotech International Ltd. is providing some new antigens by contract manufacturing, such as through a contract with Wyeth Pharmaceuticals for filling of Hib vaccine, as well as developing products through technology licensed from the US National Institutes of Health (NIH) (e.g. rotavirus vaccine clones). They have patented their process for purification of hepatitis B vaccine, and are collaborating with Indian and US organizations for an additional rotavirus vaccine and a malaria candidate product.

Biological E is an older company which has recently increased investment in vaccines. They have a number of technology transfer and licensing agreements including with Chinese research institutes for hepatitis A vaccine, with Intercell for a new Japanese encephalitis vaccine, and with the International Centre for Diarrheal Disease Research in Bangladesh for cholera vaccine [13]. In addition, they are working with the Netherlands Vaccine Institute (NVI) for development of a Hib-containing combination vaccine. They have licensed dengue vaccine technology from the NIH. Most collaborations are with small biotech companies, based on profit sharing and division of world territory, including several license agreements.

Panacea Biotech has a significant research facility and experience in intellectual property management. They are currently marketing a liquid DTP–Hep B–Hib vaccine developed with their own hepatitis B vaccine, which is a technology transfer from Heberbiotech in Cuba, and using imported DTP and Hib bulks from Chiron (now Novartis Vaccines and Diagnostics). Both arrangements are covered by joint venture agreements. However, the agreement with Novartis has limited their access on the global market. In addition, they have several license agreements with research institutions, including with NIH for dengue.

Serum Institute of India tends not to enter agreements with multinational companies (MNCs) as it wants to control the process and the market. Their work in the past has concentrated on scaling up known vaccine technologies to allow lower prices: they have to date developed and pre-qualified all the original EPI vaccines with the exception of OPV, as well as hepatitis B. In addition, they sell a pre-qualified DTP–hepatitis B vaccine on the global market. They also have an approved Hib vaccine with technology developed in collaboration with the NVI. Their pentavalent vaccine has been submitted for marketing approval in India, and for WHO prequalification. They are developing a new conjugate

meningitis A vaccine, which is now in phase two clinical trials in Africa, in collaboration with the Meningitis Vaccine Project, and an aerosol measles vaccine, in collaboration with WHO and ICMR. In addition, they have several R&D vaccine projects for which they are developing the technology in-house.

Founded to develop the first Indian recombinant vaccine, hepatitis B vaccine, Shantha Biotechnics Ltd. now sells a prequalified DTP–hepatitis B vaccine on the global market, which is also a product of their own research. They have an agreement with the International Vaccine Institute (Seoul) for the development of cholera and typhoid vaccines, and with Green Cross Vaccine (Korea) for distribution of Japanese encephalitis B vaccine in India [13]. Besides having their own research and process development activities, they also have a number of licensing and technology agreements, as well as marketing agreements. The recent acquisition of a majority stake in Shantha by the Alliance Mériex may have implications for the company's innovation strategy.

3.3. IPR management

It is important for emerging vaccine manufacturers to understand the intellectual property context in which they operate. This does not mean just understanding the national patent law, although that may be necessary. It means having the ability to form sound judgments about whether a product would be infringing and whether particular patent claims are valid. Failure to understand the IP context might result in patent infringement and potentially in liabilities for damage, which could force the manufacturer to stop selling to certain markets or to accept licensing agreements at unfavorable terms. It could also result in undue cautiousness, delaying product line expansion and missing opportunities to develop new products.

We were thus interested in the capacities of emerging manufacturers in terms of IP management. Five of the seven visited manufacturers had patent applications both in their home countries and abroad, but the remaining two had filed no patent applications. Three had in-house intellectual property specialists, while an additional two were strengthening their capacities in this area.

Using a framework from Granstrand [14], we can represent the relative degree of sophistication of the visited manufacturers. What emerges from this picture is a considerable heterogeneity among manufacturers, with some manufacturers having good capacities in IP management while others are not so well prepared in this area (Table 1).

3.4. Technology transfer

In general, a lot of technology transfer is taking place. Most manufacturers interviewed had entered partnerships with other entities. Such agreements may be the fastest route to develop a product and to get around issues of access to technologies and know-how; on the other hand they may limit

Table 1
Evolution of IP management policies in Brazil and India

Stage in the evolution of corporate IP policies	Emerging manufacturers visited
1. IP ignored Between 1 and 2	×
2. IP issues left to legal department; rewards for patents Between 2 and 3	××
3. Selective patenting and licensing; review of patent positions Between 3 and 4	××
4. IP at the heart of corporate strategy; technical staff rotate through IP department; licensing based on business and technical assessment; comprehensive trade secret policies	×

Stages in the evolution of corporate IP policies adapted from Granstrand [14]. Positioning of emerging manufacturers based on information collected during the on-site visits.

markets. When this is done with MNCs, it consists mainly of filling bulk, and restricts the firm to its own and neighboring markets for that product. This path is therefore followed only for very specific reasons such as obtaining a cell line, or as a means of financial sustainability until the company is able to launch its own innovative products. Of the seven manufacturers studied, five had technology transfer agreements with MNCs, accounting for a mean of 22% of their pipeline products [9].

On the other hand, partnerships with small biotechnology firms as well as with research institutions involve more equity of benefits and result in an effective transfer of know-how. Hence, partnerships or other types of agreement with entities such as the US National Institutes of Health, as well as collaborations with academic institutions, represented an important share of those partnerships. In the study referred to above, of the seven manufacturers visited, all had academic or research institution partnerships, which accounted for 70% of their pipeline products [9].

From the point of view of those transferring the technologies, for example, MNCs, the emerging suppliers may provide expanded access to local markets, additional manufacturing capacity, and, in countries with strong national regulatory authorities, an additional regulatory pathway for vaccines destined for the developing market. For biotechs and academic institutions, they can provide access to production and scale-up facilities and know-how. So it is no surprise that such agreements are common.

Table 2 summarizes some of the vaccine technology transfer agreements in progress in Brazil. Because of the Brazilian manufacturers' historical primary focus on the Brazilian public sector market, limitations in market were not of primary concern. Thus, these agreements tended to be with MNCs.

The characteristics of technology transfer agreements will differ depending on how they are structured, and the aims of both the technology recipient and the technology holder.

Table 2
Technology transfer agreements for vaccines in Brazil

Licensors	Licensee	Object of the contract	Year	Transfer of know-how included in the agreement?	License for patent rights included in agreement?
GSK	FIOCRUZ	Production of Hib vaccine in Brazil	1998	Yes	No
Sanofi-Pasteur	Butantan	Production of influenza vaccine in Brazil	1999	Yes	No
Biken, Japan	FIOCRUZ	Production of measles and rubella vaccine in Brazil	2000	Yes	No
GSK	FIOCRUZ	Production of MMR vaccine in Brazil	2003	Yes	No
NIH	Butantan	Exploratory license for a rotavirus vaccine	2005	No	Yes

Source: INPI [Brazilian patent office]. Publicly available information.

Table 3
Aspects of technology transfer as a means of accessing vaccine technologies or products

Type of agreement	Bulk import	Partnership	License in new product technology
Aim of technology recipient	To provide a product for local use as rapidly as possible	To develop ability to produce a particular technology	To license a new technology that will contribute to a new product
Aim of technology holder	May be humanitarian or donor driven, or to access a specific market	Advantages of expanding markets, sharing manufacture facilitated by partnerships	Royalties, or there may be a humanitarian component
Level of production and QC support from technology holder to recipient	Varies depending on characteristics of the agreement	Constant from technology holder to recipient including provision of equipment and specifications, milestone-based	Protocols and reference reagents, process development needed, royalty only
Control over eventual market by technology recipient	Generally limited to local market	Negotiated, but often limited to local market	Royalty payment is only constraint unless markets limited by prior agreements
Ability of recipient to pass on technology	None	Possibly to sell bulk, provide QC, advice	Yes, unless limited by prior agreements
Ability to produce independently	Little to none, although it may evolve	Yes, based on meeting milestones	Yes
Examples	Bio-Manguinhos with GSK for OPV, MMR; Bharat with Wyeth for Hib	Serum Institute with Meningitis Vaccine Project for meningitis A conjugate; Butantan with Sanofi Pasteur for influenza vaccine	Several manufacturers with US National Institutes of Health for rotavirus clones

Table 3 provides an analysis of several types of these agreements.

4. Impact of TRIPS on development of Hib-containing vaccines: a case study of activities in India and Brazil

To illustrate the results cited above, we have developed a case study on access to technologies for combination vaccines containing DTP. All manufacturers interviewed either produced combination vaccines or have them in their pipeline. Manufacturers described the processes and compositions they were using for producing their product. A GSK patent granted in the US and Europe on the use of aluminum phosphate, useful for developing the combination, was mentioned by several manufacturers. Most have been using the methodology for several years already, which might lessen the impact of a limiting patent.¹⁴ Also, this patent has been successfully opposed in Europe which diminishes its usefulness worldwide (as it is more likely to be found invalid in courts or patent

offices in other jurisdictions). Technologies are developed by some firms to improve yields, processes which might ultimately be patented by those firms depending on opportunity and expected returns.

Conjugation technologies that companies have used are those that are in the public domain (the so-called “Robbins” technology), or that have been transferred to them (e.g. by NVI). Patents are therefore not an issue in the sense that they can use some technology, albeit not necessarily the most efficient one. It was mentioned that the efficient conjugation systems are covered by patents, and considering that an important factor in the vaccines field is time to market this might lead manufacturers to use a less efficient but available process rather than wait for a more efficient one and lose potential markets. Furthermore, one manufacturer mentioned a patent issue on recovery after conjugation.¹⁵

4.1. Different methods used to access technologies

The manufacturers studied accessed the technology for Hib-containing vaccines in different ways: some have imported bulk with eventual technology transfer; others have

¹⁴ Manufacturers having made substantial investment will be able to continue using the product if and when the patent is granted in India, upon payment of a reasonable royalty, and without being liable for retroactive damages.

¹⁵ A patent by Aventis (now Sanofi Pasteur) on purification.

imported bulks and formulated them themselves while negotiating a marketing agreement; a third option is collaboration with a public sector organization in a technology transfer agreement; and the final option is developing the technology oneself with the possibility of licensing in patented steps or products. All these approaches have been used.

4.1.1. *Importing bulks with eventual technology transfer*

This is the approach used by Bio-Manguinhos with GSK. The Brazilian MOH wanted to add Hib vaccine to the national immunization program. Bio-Manguinhos had a long experience in partnership with GSK, who had a Hib vaccine on the market. There was no patent on the technology (at least in Brazil) but it would have taken too long or it would have been too difficult for Bio-Manguinhos to develop the product it on its own. At the time (1998), GSK had limited lyophilization capacity, thus their available finished product would not have been sufficient for the Brazilian market, while Bio-Manguinhos had extra capacity in a large filling and lyophilization facility. One of the main features of the agreement is that for 5 years, Bio-Manguinhos would manufacture a vaccine made from bulk imported from GSK. Sales of this vaccine are restricted to Mercosul¹⁶ countries, sales to other countries being subject to negotiation with GSK. The reference price in this agreement is the PAHO revolving fund price, since this is the price that the Brazilian Ministry of Health would pay for the final product. Bio-Manguinhos pays GSK this price minus a discount for the bulk, which allows Bio-Manguinhos to pay for the costs of quality assurance, scale-up, etc. and to generate some cash. In exchange for this, Bio-Manguinhos obtains the transfer of technology with technical assistance so as to be able to produce its own product. For 10 years from the signature of the agreement Bio-Manguinhos has to maintain secrecy on the specific technological know-how and cannot export outside Mercosul without GSK permission. Finally, Bio-Manguinhos has to pay 4–5% running royalties (but no fixed fees) on its own products for 5 years once it starts to sell (this is the maximum possible under Brazilian law governing technology transfer). Both parties are pleased with the outcome of this agreement. The Hib monovalent product, now made totally in Brazil, has been submitted to ANVISA for marketing authorization.¹⁷ The pentavalent product with Bio-Manguinhos-produced Hib vaccines is expected to go into clinical trials in September 2007.

4.1.2. *Importing bulks for formulation and marketing*

Bharat Biotech International has imported Hib bulks from Wyeth, performing formulation and filling, then selling on the Indian private sector market. The marketing agreement

allows them to sell in a limited number of other countries, including the Republic of Korea, which has separately approved the product based on their own inspection of Bharat. The product is not under consideration for the public sector market in India, and, in fact, will likely soon be phased out, as Wyeth is no longer producing the bulk vaccine. Bharat has said that they have developed their own monovalent Hib vaccine (tetanus conjugate) which they plan to combine with their hepatitis B and imported DTP.

Panacea Biotec has been importing DTP and Hib vaccine bulks from Novartis, and has developed a liquid pentavalent vaccine that is approved for marketing in India by the Indian Drugs Controller General. This formulation is similar to that used in another product using the Novartis bulks, that produced by Berna Biotech Korea Corp., using their own hepatitis B vaccine and Novartis's DTP and Hib vaccines, also in a liquid formulation. The latter product is now pre-qualified and offered for sale on the global market; however, Panacea's agreement restricts the sale of their product to the Indian market.

The satisfaction this type of agreement brings to those importing the bulks depends on the characteristics of the negotiated market for the product. This approach differs from a classical technology transfer agreement in the extent of control the producer of the bulk products has over the characteristics of the final product and the ability of the bulk purchaser to actually produce the bulk vaccine; generally manufacturers with this much control over the process are in a business rather than a dependent relation with the bulk suppliers.

4.1.3. *Collaboration with a public sector institution for technology transfer*

Both Serum Institute of India and Biological E are using this route, both collaborating with the NVI for transfer of the Hib technology, and formulating the product for use with their own DTP and hepatitis B to make a pentavalent vaccine. Serum's tetravalent vaccine, DTP–hepatitis B, which is used as a solvent for the lyophilized Hib, is already pre-qualified, and their Hib is also approved for marketing in India. The pentavalent vaccine has been submitted for marketing approval and subsequent prequalification. Biological E is further behind, but has an approved tetravalent product and has completed clinical trials on the pentavalent vaccine, which they expect to be approved soon.

The technology transferred by the NVI was developed by them in the Netherlands, and then transferred to India. It involved the Robbins conjugation technology, which is in the public domain, despite the fact that there may be better conjugation technologies. The manufacturers going this route mentioned several instances in which they “innovated around” other steps in the production process which might possibly be covered by existing patents which has caused some delays. Nevertheless, the two manufacturers now have products that have potential markets, both in India and globally, and are confident that the technology they have used

¹⁶ The Portuguese term for the economic cooperation between Argentina, Brazil, Uruguay, Venezuela and Paraguay; in Spanish it is Mercosur.

¹⁷ Maria da Luz Fernandez Leal, Bio-Manguinhos, personal communication, June 2007.

is without restrictions, because the agreement with the NVI assured that NVI would cover that risk.¹⁸

4.1.4. *Developing the technology in-house*

Three manufacturers in the study, Bharat, Butantan and Shantha, have said that they are developing Hib-containing products through their own research processes. The available information on the Bharat process has been included above. Both Butantan and Shantha produce DTP and hepatitis B, so both would theoretically be able to produce a pentavalent vaccine. Shantha has already a DTP–hepatitis B combination vaccine which is prequalified and available for sale on the global market. Shantha is said to have obtained some of the technology for the combination vaccine from Berna Biotech Korea Corp.,¹⁹ and these liquid Hib-containing products have been approved for marketing in India. It is not known at what stage the Hib development projects of the other two manufacturers are, in both cases, they would have to explore the patent landscape to ensure that the technology they are using is free of infringement. In the absence of in-house expertise, this becomes more difficult, and is the major liability mentioned by emerging manufacturers to developing the technology themselves.

5. Conclusions

This study analyzed the issues confronting vaccine manufacturers in two large developing countries to develop new and more innovative vaccines, and outlined how they have accessed the relevant technologies. Emerging suppliers considered in this study have used three options.

The first option is to develop the product oneself. This has the advantage of leaving the manufacturer in full control of the technology but is generally a slower way to develop a new vaccine. It also requires that this manufacturer has freedom to operate, i.e. that no blocking patent is in force in the relevant country. To save time and cost, emerging suppliers have very often preferred to enter into technology transfer agreements (options 2 and 3). Several of them have independently developed a hepatitis B vaccine. However, independent emerging supplier research efforts have so far not led to a licensed and prequalified innovative product for developing country use.

The second option is to license in technology, know-how and patent rights, generally from industrialized country academic or public institutions. This involves complementary in-house development on the part of the emerging supplier. Freedom to operate is less of an issue in this case as the agreement would include a license to the rights of the technology licensor. However, patent rights from third parties may still be blocking. Option 2 has been extensively used where

the interests of these public institutions (access to production capacity) and developing country vaccine manufacturers (access to technology) have often converged.

The third option is to enter into agreements with MNCs for importation of bulk for local finishing, sometimes accompanied by transfer of know-how and technology for complete production. Agreements differ in which partner has responsibility for quality control and whether it will result in the transfer of the ability to actually produce the bulk vaccine. Freedom to operate for the emerging supplier is unlikely to be an issue here because the MNC has presumably secured freedom to operate for itself. From the MNC perspective, these agreements have the advantage of guaranteeing access to large protected markets. The drawback is a potential risk to the MNC reputation and intellectual property. From the developing country perspective, the advantage of this approach is the rapid ability to bring the technology in-house and to have the product on the market. The drawbacks are the potential limitations in the market and eventual ability to control the technology.

It is clear that discussions around TRIPS have resulted in increased IPR awareness and expertise among the emerging suppliers studied. Due to late TRIPS implementation in India and the backlog in Brazil, few patents have actually been granted under the new patent laws, so that the effects of TRIPS are to a large extent yet to be felt. Thus, it is difficult to evaluate what the impact of TRIPS will be on technology access and innovation for these manufacturers.

As more patents are applied under the new TRIPS-compliant laws, securing freedom to operate will become a larger issue. Thus, it is expected that emerging suppliers will resort more frequently to technology transfer and licensing agreements. However, patent considerations will no longer be secondary in these agreements. For both independent and collaborative efforts, a good understanding of intellectual property and intellectual property management is now critical for developing country institutions.

Acknowledgements

The authors acknowledge with pleasure the contributions of Mariam Ayass, who was part of the study of Indian manufacturers, and of Richard Mahoney, for constructive comments on the manuscript.

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¹⁹ Now taken over by Crucell, which may limit the use of this technology.

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