



A Fair Shot for Vaccine Affordability

**Understanding and addressing the effects
of patents on access to newer vaccines**

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Executive Summary

This report considers the effects of patents on access to pneumococcal conjugate vaccines (PCV) and human papillomavirus (HPV) vaccines – two important, yet expensive, new tools to protect people from preventable sickness and death. As new vaccines have been developed and recommended for all children worldwide, they have come with high prices, dramatically increasing the cost to fully immunise a child. Due partly to high prices, many countries have not introduced these lifesaving vaccines. This analysis finds that there are both many types of patents and a significant quantity of patents and patent applications which together pose a threat to access to affordable versions of newer vaccines, like PCV and HPV vaccines. We also find that there are measures which potential competitor vaccine manufacturers can take to mitigate some of the harmful effects of patents on competition and access. In addition to these measures available to potential vaccine manufacturers, governments and other stakeholders can also help promote price-lowering competition for lifesaving vaccines for children worldwide.

Analysis and findings

The key finding of this work is that patents pose a threat to the timely development of and access to affordable versions of newer PCV and HPV vaccines. In addition to blocking patents, there are numerous patents that increase uncertainty, costs and delays in competition for vaccines.

Potential competitor vaccine manufacturers have several options to address these barriers, each offering different benefits and limitations. For example, vaccine manufacturers can licence-in, ‘design around,’ or challenge patented technology. However, understanding the patent landscape is a difficult, costly and time-consuming prerequisite for any action.

The extent to which access to affordable vaccines is enabled and promoted through competition also varies due to differences in the political and legal environments in which manufacturers operate. Variations in patent laws and their interpretation may also impact how barriers to access can be overcome. Countries have the option of adapting and using law and policy flexibilities to promote competition and access. For instance, choosing to implement stricter patentability criteria creates an enabling environment for patent oppositions, patent revocations and the use of compulsory licences. Other stakeholders can also play a role in supporting competition and affordable access to vaccines.

Introduction

As an international medical humanitarian organisation, vaccination is a key part of Médecins Sans Frontières (MSF)'s work. Each year, MSF teams vaccinate millions of people, both as a response to outbreaks of diseases such as measles, meningitis, yellow fever and cholera, and through routine immunisation activities in projects where we provide health care to mothers and children. In 2015 alone, MSF delivered about 5.3 million doses of vaccines and immunological products in over thirty countries.¹

Through our operations, MSF teams vaccinate thousands of vulnerable children each year against pneumonia, the number one killer of children under five years worldwide. MSF is also starting to provide vaccinations against human papillomavirus, a sexually transmitted infection that can lead to cervical cancer, one of the leading cancer killers of women in developing countries. The World Health Organization (WHO) recommends vaccination with the pneumococcal conjugate vaccine for all children worldwide and human papillomavirus vaccination for girls worldwide. However, these vaccines are often unaffordable for developing countries. Millions of children around the world are left unprotected from pneumonia or HPV when Ministries of Health cannot afford to incorporate these vaccines into their national immunisation programmes.

Pneumonia

Globally, pneumonia kills nearly one million children every year.² Children in crisis-affected contexts are particularly susceptible to pneumonia, and MSF medical teams often see its deadly effects in our health facilities. The pneumococcal conjugate vaccine (PCV) can prevent many cases of pneumonia and is currently manufactured for children by just two companies: Pfizer and GlaxoSmithKline (GSK). Unfortunately, PCV is priced out of reach of many parents, governments and treatment providers, due in part to high prices caused by a lack of sufficient competition. Approximately one third of the world's countries have not been able to introduce PCV because of its high price.³ Millions of vulnerable children living in countries such as Jordan, Thailand and the Philippines are left without affordable access to this life-saving vaccine. According to 2015 WHO/UNICEF estimates, 60% of the world's infants (81.6 million) were not receiving PCV in 2015, either because they lived in one of 55 countries that had not yet introduced the vaccine, or they were not being reached by the routine immunisation services in their country.

MSF provides PCV through our work in countries such as Central African Republic, Ethiopia, Greece, South Sudan, Syria and Uganda, among others. From 2009 to 2014, MSF negotiated with Pfizer and GSK to obtain a sustainable, affordable price for PCV, exceptionally accepting a limited-term donation, with agreement from both Pfizer and GSK that they would work on longer-term solutions to improve affordability. In the absence of such a solution, MSF and other humanitarian organisations continued to struggle to purchase PCV at an affordable price. For example, in 2016 MSF paid 60 Euros (US\$68.10) for one dose of the Pfizer product to vaccinate refugee children in Greece – 20 times more than the lowest PCV price offered by Pfizer and GSK.

In 2015, faced with the impossibility of obtaining an affordable price, MSF launched a public campaign – *A Fair Shot* – calling on both companies to lower the price of PCV for humanitarian use and in all developing countries. Because of this pressure, in late 2016, both Pfizer and GSK finally agreed to extend their lowest global price to humanitarian organisations vaccinating in emergencies, but not to developing countries more broadly.⁴ Many governments, providers, and parents still struggle to afford PCV.

Human papillomavirus

The World Health Organization (WHO) estimates that more than one million women are living with cervical cancer worldwide, most often as a “consequence of a long-term infection with human papillomavirus (HPV).” WHO also notes that most cases occur in developing countries;⁵ in 2012, more than a quarter of a million women died from cervical cancer in developing countries.⁶

Two companies, GSK and Merck, manufacture vaccines that protect against two (GSK), four and nine (Merck) different types of HPV. Types 16 and 18 are associated with 71% of cases of cervical cancers and are present in all three vaccines.⁷ Despite the importance of this vaccine, by mid-2016, only 65 countries had introduced HPV vaccines.⁸ Prices for the vaccines range from \$4.50 per dose at the lowest global price up to \$193 per dose in the US private sector.⁹ In contrast, based on peer-reviewed manufacturing estimates, HPV vaccines could be manufactured for as little as \$0.50 to \$0.60 per dose.¹⁰

MSF provides cervical cancer screenings and HPV vaccines in some projects, for example in the Philippines, and is preparing to do so in Zimbabwe.

Report scope and methods

This report considers how patents affect the pace of follow-on development and competition of vaccines, specifically in the cases of PCV and HPV vaccines, and how these patent barriers can be managed to best promote affordable access to vaccines. Other factors also contribute to the current duopoly situation in the PCV and HPV market and the lack of sufficient price-lowering competition. For example, issues such as an appropriate regulatory pathway and market dynamics of vaccine manufacturers may also affect competition. Those and other issues are not included in the scope of this report, but also merit consideration in how to best promote affordable vaccine access for all. This report is focused specifically on vaccine patents and their effects.

For the purposes of this report, MSF has conducted PCV and HPV vaccine-related literature and patent reviews, as well as in-country interviews with manufacturers and governmental and non-governmental organisations in Brazil, China, India and the US. The report does not intend to provide a comprehensive patent landscape analysis of the two products of concern.

The focus of this analysis was on patents held by originator companies and possible responses by potential competitors. In response to these patent barriers, competitors may develop new approaches to manufacturing these vaccines and may also seek patents on their own processes. We neither searched for nor analysed these patents, but a future project could be dedicated to understanding the extent to which competitor manufacturers are seeking patents, and what effect this may have on vaccine affordability and access in the longer term.

Our literature review includes an extensive set of documents, including confidential vaccine technology patent review documents and non-confidential literature such as published journal articles and reports examining the impact of intellectual property (IP) on access to medical technologies and public health. The non-confidential sources were found through searches on PubMed and Google Scholar. When necessary, we also performed our own patent searches using the following terms in various combinations: ‘pneumococcal’, ‘conjugate’, ‘PCV’, ‘papilloma’, ‘VLP’ and ‘genotype’. For this, we used the following patent databases: WIPO PatentScope, ESPACENET, and the public search databases of the Brazilian Patent Office [INPI], the Chinese Patent Office [SIPO] and the Indian Patent Office.

This analysis is further supplemented by the information gathered through a series of semi-structured key informant interviews with representatives from 15 manufacturers and 5 governmental, intergovernmental and non-profit organisations and others in Brazil, China, India and the US, in person or via telephone, between August 2014 and May 2015.

The semi-structured interviews were based on a set of questions^a that we sent to the key informants prior to an in-person meeting. Due to the confidentiality of some of the issues discussed, interviewees and their affiliated organisations will not be disclosed.

^a See sample interview questions in Annex 1.

Key findings

Intellectual property undermines competition and keeps prices high

As MSF has seen repeatedly for medical products critical to our operations, competition among multiple manufacturers is a proven way to reduce prices and increase access. Without competition, single suppliers can set prices high, and limited supply options leave vulnerabilities, including dependence on a sole manufacturer's ability to maintain consistent supply. The effects of IP monopolies like patents on competition and supply for pharmaceutical products are well documented.^{11,12,13} Yet, as increasingly recognised, and discussed in more detail within this document, patent-based monopolies can also be a barrier in the field of vaccine production and have posed challenges to vaccine development for decades.

Traditional narrative of technology transfers and lack of consideration of patent barriers

Prior experiences of developing vaccines for diphtheria, whole-cell pertussis, polio, measles, mumps, influenza, rubella, and yellow fever in World Bank-classified low- and middle-income countries had suggested that patents do not play a major role in modifying the behaviour of vaccine manufacturers. Historically, these vaccines have been developed using conventional egg-based and cell culture-based methods generally not protected by patents. In these cases, the process of manufacturing and key 'know how'^b was considered a barrier to entry for new competitors.¹⁴

When looking at the manufacturing experiences of some older vaccines, this perception is an oversimplification. The development of the hepatitis B vaccine, for example, dating back nearly half a century, faced patent barriers resulting in monopolies and high prices.¹⁵ The two manufacturers of recombinant hepatitis B vaccines, Merck and SmithKline Beecham, needed licences to more than 90 patents from universities, public institutes and private companies to produce their vaccines. Despite the contributions of publicly funded R&D, product prices at introduction were as high as \$40 per dose for this 3-dose regimen (equivalent to more than \$87 per dose in real terms in 2016).

Patents are increasingly an issue for development of newer vaccines

Patent activity in the field of vaccine development and manufacturing has been increasingly recognised as problematic over the past 15 years, according to manufacturers interviewed for this report. International organisations with vaccines expertise such as WHO and Gavi, the Vaccine Alliance, have similarly noted that patent thickets are an increasing concern for vaccines.¹⁶

For medical products such as PCV and HPV vaccines, patent barriers can slow the development process, increase costs, increase uncertainty and deter or even block other manufacturers considering entering the market.¹⁷ A recent analysis by Chandrasekharan et al. found 106 Patent Cooperation Treaty (PCT) applications "potentially relevant to the manufacturing of pneumococcal vaccines"^c and 93 patents applications "relevant to the manufacturing of HPV vaccines."¹⁸

The patent applications and discussions with manufacturers indicate that broad monopolies are being pursued for these vaccines, through tactics such as using overly general language in patent claims concerning the scope of the inventions. According to national criteria, many of these patents or applications could be challenged or rejected due to their weak technical merits. With patents sought for PCV and HPV vaccine technology in major and emerging markets, like Brazil, China, Europe, India, and the US, governments and other stakeholders

^b Confidentially held, or 'closely held,' information in the form of unpatented inventions, formulas, designs, drawings, procedures and methods, together with accumulated skills and experience, privately maintained expert knowledge on the operation, maintenance, use/application of vaccines and of its sale, usage or disposition.

^c Examples of possible blocking patents and applications concerning PCV are described in Annex 2.

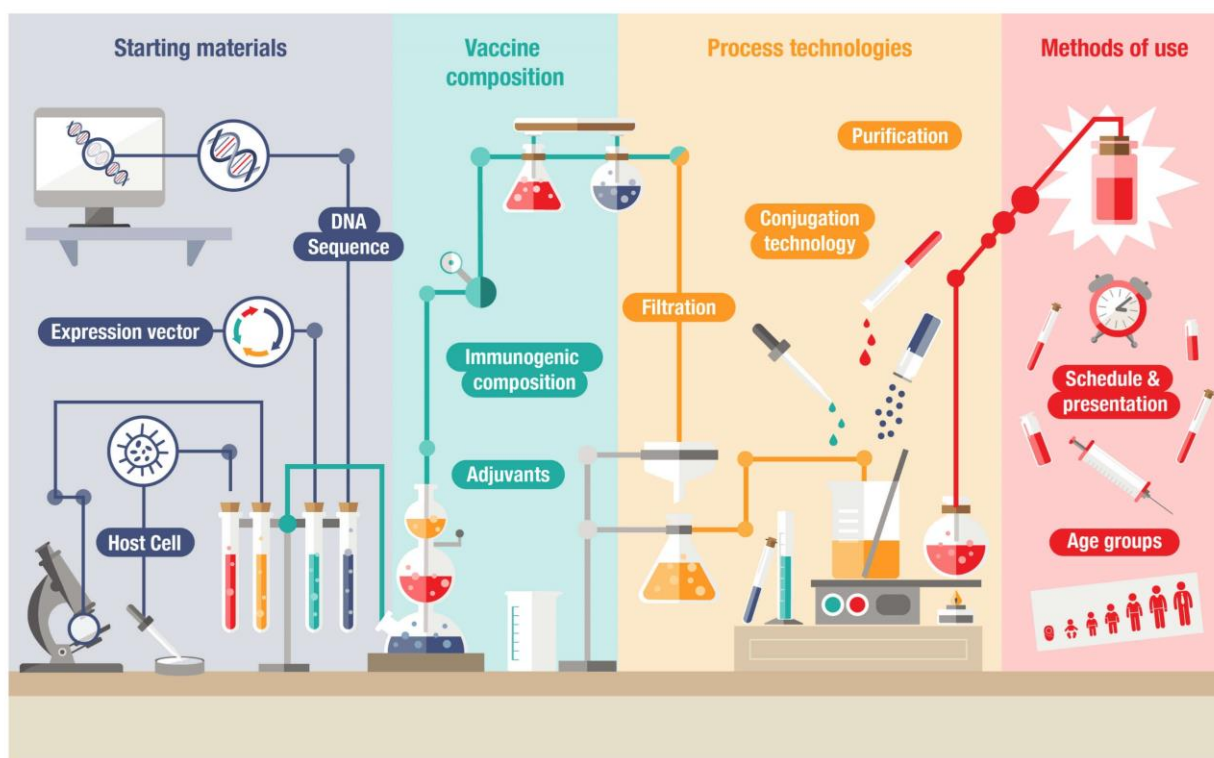
seeking to encourage competition and access to affordable vaccines must consider how to mitigate the constraints that pending and granted patents in developing countries place on the ability of potential competitor vaccine manufacturers to develop or sell competitor vaccines.

Patents undermine competition throughout PCV and HPV vaccine manufacturing and beyond

Patents can act as barriers throughout vaccine development, manufacturing and administration processes. PCV and HPV vaccine products are protected by a series of patents and patent applications, covering all aspects including starting materials, composition, process technologies, and methods of using vaccines, including age groups, vaccine presentations and schedules. Potential competitor vaccine manufacturers considering entering the market may face patent challenges “in any step of the development process starting from preclinical R&D, to scale up, formulation and licensure in the markets of choice, and hence may alter their decision pathways... at each step.”¹⁹

The typical strategy for a vaccine manufacturer seeking a patent monopoly is to use broad, non-specific claim language to define what they claim is the invention. Many of those patents and applications do not merit patent protection according to national laws, and many are used mainly to maximise the scope of monopoly.

Figure 1:
Examples of Patent Barriers Throughout the Vaccine Development Process and Beyond



Starting materials

Starting materials patents cover the inputs/initial ingredients for making a vaccine, including various chemical reagents, host cells, vectors, and DNA and/or RNA sequences of various types. These inputs are highly likely to be required for vaccine production. If the rights to use these materials in vaccine manufacturing are not obtained by a company, it may be very difficult to ‘design around’ the need for these materials. These materials have often been patented years ago and they may now be in the public domain, as is the case for PCV and HPV vaccines.

Several patent applications were filed on HPV vaccine starting materials from the mid-1990s. For instance, Merck filed a patent application on the basic HPV DNA,²⁰ covering the most common antigen types HPV 16 and HPV 18. The application attempts to protect recombinant DNA sequences encoding the important antigenic proteins of papillomavirus and purified virus-like particles comprised of the recombinant proteins. It also tries to cover the methods of making and using the recombinant proteins. Merck additionally filed a patent application seeking monopoly protection over virus-like particles containing HPV 18.²¹ Where granted as claimed, these patents could block anyone who plans to develop alternative HPV vaccines during the patent term. These two Merck applications, where granted, should have started to expire around the world beginning in 2015-2016.

A number of newer patent applications since the 2000s on HPV vaccines are also related to starting materials. It is a common practice to file such ‘second-generation’ applications to seek additional commercial advantages. For instance, GSK filed a patent application²² claiming modified DNA sequences of HPV which provide enhanced levels of expressed antigen. This patent would expire in 2023 where granted. Another example is a GSK patent application²³ related to cross-reactivity, where HPV 16 and HPV 18-containing constructs can be used in a vaccine that protects against other HPV antigens besides 16 and 18. The detailed effects of these newer patent applications on follow-on development of alternative HPV vaccines require further analysis.

Vaccine composition

Vaccine composition patents typically seek to cover the resulting combination of immunologically important parts of the vaccine, plus associated materials, such as adjuvants, buffers and preservatives. These types of patents can potentially have strong blocking effects.

One of the key patents that Pfizer is seeking for its PCV13 product relates to the vaccine’s composition.²⁴ See more details on this PCV13 patent application and why it represents an unwarranted obstacle to price-lowering competition for PCV in the PCV13 patent opposition case study.

There are numerous other examples of vaccine composition patents and these may also warrant further analysis for the effects they may have on competition. For example, Pfizer, GSK and other companies have further filed a series of patent applications claiming different aspects of PCV compositions including those covering up to 20 and 26 valent PCV vaccines.²⁵

Process technologies

Patents related to vaccine process technologies grant monopolies on the way a vaccine is manufactured. The specific manufacturing methods depend on the type of vaccine. Many different patents and patent applications have been identified that cover or attempt to cover various aspects of vaccine process technologies.

For example, basic conjugation technology needed for PCV manufacturing is patent protected in at least six countries.²⁶ This patent is broad and non-specific, blocking competitors from using a general process for combining several vaccine elements (a polysaccharide, e.g., derived from a *Pneumococcus*, activated with a specific organic compound and then joined to a carrier protein) to obtain a conjugated immunogenic product. These patents have already begun to expire as of 2016. Until expiry, a vaccine manufacturer wanting to offer a more affordable PCV is required to address this barrier in countries where the patent has been filed or granted.

Some other examples of patents filed by different applicants claiming different process technologies related to PCV production may also warrant further analysis to assess their potential impact on competition for PCV vaccines.²⁷

Methods of using vaccines

‘Methods of use’ patents seek a monopoly on the way a product is used, for example how a vaccine is administered to children. Depending on specific claim language, this can include patents on various vial

presentations, dose regimens, populations or age groups covered, other elements related to the presentation and packaging of the vaccine itself, or the use of the vaccine in people.

These patents are highly problematic because they may undermine the ability of Ministries of Health and clinicians to practise medicine and immunise children in the most appropriate way, free from any potential patent infringement risks. Additionally, these patents may also make potential competitors liable if their product labels and package inserts include information of dosage regimen or method of use that are under the scope of the concerned patents. This can be the case even if more affordable competitor vaccine products themselves do not infringe on originator's patents on a given vaccine.

One example of this is a GSK patent application²⁸, which essentially seeks a monopoly on administering a PCV after a child has received tetanus and/or diphtheria vaccines.^d This 'preimmunisation' claim term is particularly broad; many national immunisation programmes could have a national vaccination protocol through which a child may receive tetanus or diphtheria vaccines before getting PCV.

If granted, this patent may have a strong blocking effect on the use of any alternative PCV in national immunisation schedules. GSK has applied for this PCV patent in Great Britain^e (withdrawn), Brazil, Eurasian Patent Organisation and Morocco.²⁹ It was also filed, but subsequently withdrawn, in various other jurisdictions, including Australia, Canada, China, Germany and the European Patent Office, South Korea, and abandoned in India, following pre-grant opposition.³⁰ It has already been granted in South Africa.³¹

Patents related to age groups

Patent claims can also cover specific age groups to which the vaccine can be administered. If granted, these patents can restrict competition by blocking other manufacturers from selling vaccines for administration to the specified (and likely necessary) age groups. For example, the European Patent Office granted a patent³² to GSK for a method of using a 'two dose' HPV16/18 vaccine.³³ The patent application includes a patent claim stating that the vaccine is formulated for administration 'to a subject 14 years of age or below'.³⁴ It indicates a monopoly on immunising people who are under 14 years old, which covers the full age range of girls recommended by WHO to receive HPV vaccines.³⁵ This may well be a patent that blocks competition in Europe and prevents competitor manufacturers from offering more affordable versions of HPV vaccines that protect against these two critical strains of HPV. In its PCT application³⁶, the initial claims of the equivalent patent are even broader, covering the use of the concerned method for females aged '25 years or under', '9 to 25 years', '9 to 14 years', '15 to 19 years' and '20 to 25 years', thereby seeking to cover all possible vaccination schedules for the full ranges of ages for whom HPV vaccine would be most effective.

Patents related to vaccination schedule and presentation

Dose regimens are formalised schedules by which medicines or vaccines are administered, including the dose of the vaccine, the number of doses in a period of time and the time between doses. The patenting of these regimens, including for vaccines, effectively grants a patent holder a monopoly that inhibits the development of competitor products that may need to be administered in the same or a similar dosing regimen, and undermines the ability of medical professionals to prescribe the most medically sound regimens based on health needs.

^d More specifically, GSK wants a monopoly on immunising patients with various PCV serotypes (7, 10, 11, 13, 14) when the patient has been 'preimmunised' with tetanus toxoid, or derivative, and/or diphtheria toxoid, or a derivative.

^e GB20050026412 (European patent EP1940462), withdrawn in 2011.

For example, a GSK patent application on the HPV vaccine³⁷ contains very broad claims. The technology in this GSK patent application covers both bivalent^f and quadrivalent^g HPV vaccines and claims a process of administering a ‘two-dose regimen’ consisting of a first dose and a second dose, wherein both doses can be either bivalent or quadrivalent, covering all virus types causing cervical cancer. It is sufficiently broad to affect manufacturers who intend to move towards two-dose regimen administration for their bivalent or quadrivalent HPV products, while a two-dose schedule is currently recommended by WHO for HPV.³⁸ This patent application has been issued in Europe³⁹ for the ‘two dose’ bivalent HPV vaccine, and the vaccine was approved for marketing by the European Commission in December 2013. Applications have also been filed in Australia, Canada, China, India, New Zealand, South Korea and the US. It has been withdrawn in the Philippines and refused in Ukraine.⁴⁰

In other situations, broad claims in patent applications could also seek monopoly protection over the vial presentation and carry concerning implications for the launch of alternative versions of the vaccine by follow-on manufacturers. Vial presentation refers to the format of the vaccine, in terms of the number of doses, the volume and the weight contained within one unit of production. For example, it could refer to a single-dose pre-filled syringe, a 10-dose vial with 2 ml per dose, a 20-dose vial and so on.

Multi-dose vial presentations, where more than one dose of the vaccine is contained in a vial, are an advantage for developing country immunisation programmes because they decrease cold chain capacity requirements and ease vaccination programme logistics. Multi-dose vials, in general, also have a lower price per dose compared to single-dose vial and/or syringe formats. Pfizer filed a patent application concerning a multi-dose vial PCV13,⁴¹ which includes broad claims related to specific presentations, including pre-filled vaccine delivery devices (such as a syringe) as well as a vial container. If granted as claimed, it might effectively block the development and launching of alternative versions of multi-dose vial PCV13 and secure the market of using such presentations (multi-dose vials) for only Pfizer’s product. The monopoly associated with this patent could mean that public health programmes looking to switch to multi-dose vial PCV13 or a pre-filled ‘device,’ such as a pre-filled syringe, would either have to stay with a single dose vial format or have to use Pfizer’s version only. This patent has been granted in Australia, South Korea, the US and by the European Patent Office.⁴² An equivalent application has also been filed in China⁴³ and India⁴⁴, pending examination.

Summary

There are many different aspects of vaccines that are being patented, in many cases undeservingly so per national laws. These patents pose significant barriers for other manufacturers to enter the market and contribute to a competitive environment that could help lower prices and increase access. Taken together, these patents indicate that throughout the vaccine development process and beyond, patents pose a threat to affordable vaccines by impeding, and possibly outright blocking price-lowering follow-on competition. In some cases, potential competitors have opportunities to address and overcome these barriers providing they have the time, resources, technical know-how and an accurate assessment of the vaccine patent landscape.

^f Bivalent HPV contains L1 protein from only two main virus types, HPV 16 and HPV 18.

^g Quadrivalent HPV contains L1 protein from 4 virus types, namely HPV 6, HPV 11, HPV 16, HPV 18, all causing cervical cancer.

Strategies to address patent barriers

Strategies for potential competitor vaccine manufacturers

Potential competitor vaccine manufacturers may face multiple patent barriers in the development process in one or multiple countries where they wish to operate. However, there are several strategies manufacturers can employ to address these barriers. Manufacturers may licence-in or acquire the rights to a patented technology; design around the technology, essentially devising a new approach to producing the product that does not rely on patented technology; or challenge the key/blocking patents on needed technologies. Each approach offers its own benefits and limitations, and interested manufacturers may choose to use one or more to address any given patent barrier.

Regardless of the approach(es) employed, a strong understanding of the existing patent landscape, including in which countries a patent has been filed or granted, and of available legal and policy measures that could be used in each relevant country to overcome any existing barriers, is a complex and costly prerequisite.

Understanding the patent landscape is a prerequisite to develop effective strategies

A major challenge for manufacturers interested in developing more affordable versions of newer vaccines is that it is very difficult to develop a full patent landscape of existing patents or those under application for a given vaccine in all jurisdictions. There is no single source with comprehensive information on all patent applications that may be relevant to a given product, or in which jurisdictions those patents may have been filed or granted. Additionally, not all patents and applications will present a barrier to the development of a competitor product. The scope of technologies covered by a patent application may also differ from the granted patent because applications may contain very broad claims that do not merit protection. Those claims might be amended, narrowed, divided, rejected or opposed in the process of patent examination. Interested manufacturers will need to assess not only the patent landscape, but also the extent to which each identified patent or patent application impedes manufacture of a given vaccine in each country.

Before starting vaccine development activities, potential manufacturers may develop an IP risk analysis or so-called ‘freedom to operate’ (FTO) report. Some companies interviewed believe such diligence is an important pre-condition for getting funding or procurement commitments from donor agencies if they plan to enter developing country markets. The FTO report identifies, analyses and makes recommendations to address patents that may impede a manufacturer’s ability to produce a product, and where those patents have been filed or granted. A report can be several hundred pages long. The process requires extensive work from numerous departments of the company, including the IP team, business development team and R&D team, and often requires external professional services.

FTO reports may provide guidance to support each critical stage of R&D so that these activities do not infringe on patents, including understanding whether research exemptions will allow R&D work to progress even when a patent may exist. Broad blocking patents are specifically handled by studying prior art and validity in order to evaluate early market entry possibilities in given jurisdictions. An understanding of whether relevant patent applications or granted patents are legally valid must be conducted on a country-by-country basis, further complicating FTO analyses. The same patent sought in different countries may result in different decisions by national patent offices. This is due to differences in patentability criteria, examination practices, patent opposition procedures, and whether the country is a ‘least-developed country (LDC)’ and thus exempt under WTO rules from patenting obligations.^h

^h Least-developed countries (LDCs) are exempted from the obligation of providing patent protection on medicines until 2033, and from the general obligation of implementing the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) until 2021.

Such studies are cost and skill intensive. The complexity and resource intensity of a FTO exercise is increased by a lack of transparency of vaccine-related patenting. Publicly available search tools and databases often do not provide up-to-date information about patent status in developing countries.

Licensing-in the necessary technology

If patent barriers are identified on a vaccine technology, one option available to manufacturers interested in developing a vaccine is to licence-in the patented technology. Licensing-in patented technologies is an approach whereby interested companies can negotiate with the patent holder for permission to access patented technologies necessary to produce a vaccine under a given set of terms. Sometimes both parties have technology that the other needs. In this case, both parties may likely negotiate a so-called ‘cross-licence’ (see case study for details). Additionally, in-licensing of patented technologies or other know-how can be part of a technology transfer agreement.

Licence agreements can be highly complex, involving multiple patents on various aspects of vaccine manufacturing and use. Negotiations may involve many people (including the board of directors, deputies, business development and IP experts) and may take many months to finalise. There are several considerations for a potential manufacturer considering a licensing strategy:

1. Ensure that all the necessary technology and accompanying non-patentable know-how is provided through the agreement, requiring expert staff to assess and ensure completeness of the agreement.
2. Consider any additional costs that may be incurred in undertaking a new vaccine production route and consider the impact this will have on the production timeline, for example, if a new facility is required to utilise any transferred technology.
3. Secure options to obtain access to any other materials needed in the production process that are not explicitly covered by the agreements with the licensing party, such as specific excipients, adjuvants or host cells, either from the licensor or purchased outright.
4. Consider how to access the IP of parties not necessarily covered by the licence with a given patent-holder. For example, assume Company A has exclusively licensed-in essential IP from Company B. Company A then negotiates a licence agreement with Company C. Company C may need to go directly to Company B to try and get this important IP or, alternatively, Company A may need to re-negotiate their original exclusive contract with Company B to secure permission to licence this additional necessary IP to Company C.

Benefits and limitations

The benefits of the licensing-in approach are that manufacturers can secure access to an established technology and may not need to go through time- and resource-intensive patent oppositions or additionally cost-intensive revocations. It also avoids the risk of failure that can come with internal efforts to design around existing vaccine technology patents.

There are several limitations to this approach, including the requirement that the patentee is willing to licence-out the key patent, and that complex patent landscapes may leave prospective vaccine manufacturers unsure of whether they have licensed-in all relevant technology, especially if there is a lack of clarity on whether third-party patents are relevant and appropriately licensed.

Other limitations include:

- **Costs.** It can be expensive to licence-in technology when one company holds a monopoly due to one-time or recurring royalty payments expected by the monopoly holder in exchange for any licensing deal.

- Geographic restrictions. Prospective vaccine manufacturers are also likely to face restrictions with terms and conditions, including potential constraints prohibiting them from selling in certain countries. Country restrictions may exist even when there is a high burden of a vaccine-preventable disease or in countries with no patents in force.
- Other restrictions. These can include restrictions on termination of the licence and on challenging patents of the licensors.
- Obligations. Licence agreements may also come with a unilateral obligation of mandatory ‘grant-back’ of the new developments of the products made by the licensee during the licence timeframe. Agreements may also impose burdensome terms on the licensee, requiring them to first buy and later produce the licensor’s product, providing the multinational licensor with an essentially exclusive entry into the market of the licensee’s country. Deal durations can be much longer than is customary for vaccines, particularly if the exclusive licensee is a government-owned entity. This can pre-empt other vaccine companies from competing through licensing in the same technology.⁴⁵

Vaccine manufacturers seeking to licence-in a patented technology will need to ensure they have a clear understanding of what is included, and under what terms and obligations, before being able to assess whether this may be an appropriate strategy in developing a competitor vaccine.

Case study: cross-licensing of HPV vaccine patents

With cross-licensing, both parties have IP that the other needs. In contrast, a standard licence dictates payment and other terms granted by one party in exchange for IP held by another party. One example of complex cross-licensing negotiations involved HPV process and product technologies (vaccine inactivation, purification, disassembly/reassembly and formulation/adjuvants).

Researchers at the University of Queensland in Australia filed a patent application in the early 1990s in the U.S. on their finding that human papillomavirus L1 and L2 proteins could form virus-like particles (VLPs). In 1992, researchers at Georgetown University Medical Center in the US filed a US patent application involving substantially identical subject matter to the University of Queensland application. In 1992-1993, researchers from the National Cancer Institute (NCI) and the University of Rochester found that protein L1 from bovine papillomavirus formed VLPs that induced high levels of neutralising antibodies in immunised animals. Both Merck and GSK eventually developed these technologies to bring the vaccines to market.^{46,47}

Figure 2 (next page) describes the timeline and the relationships of licences on these three related technologies.

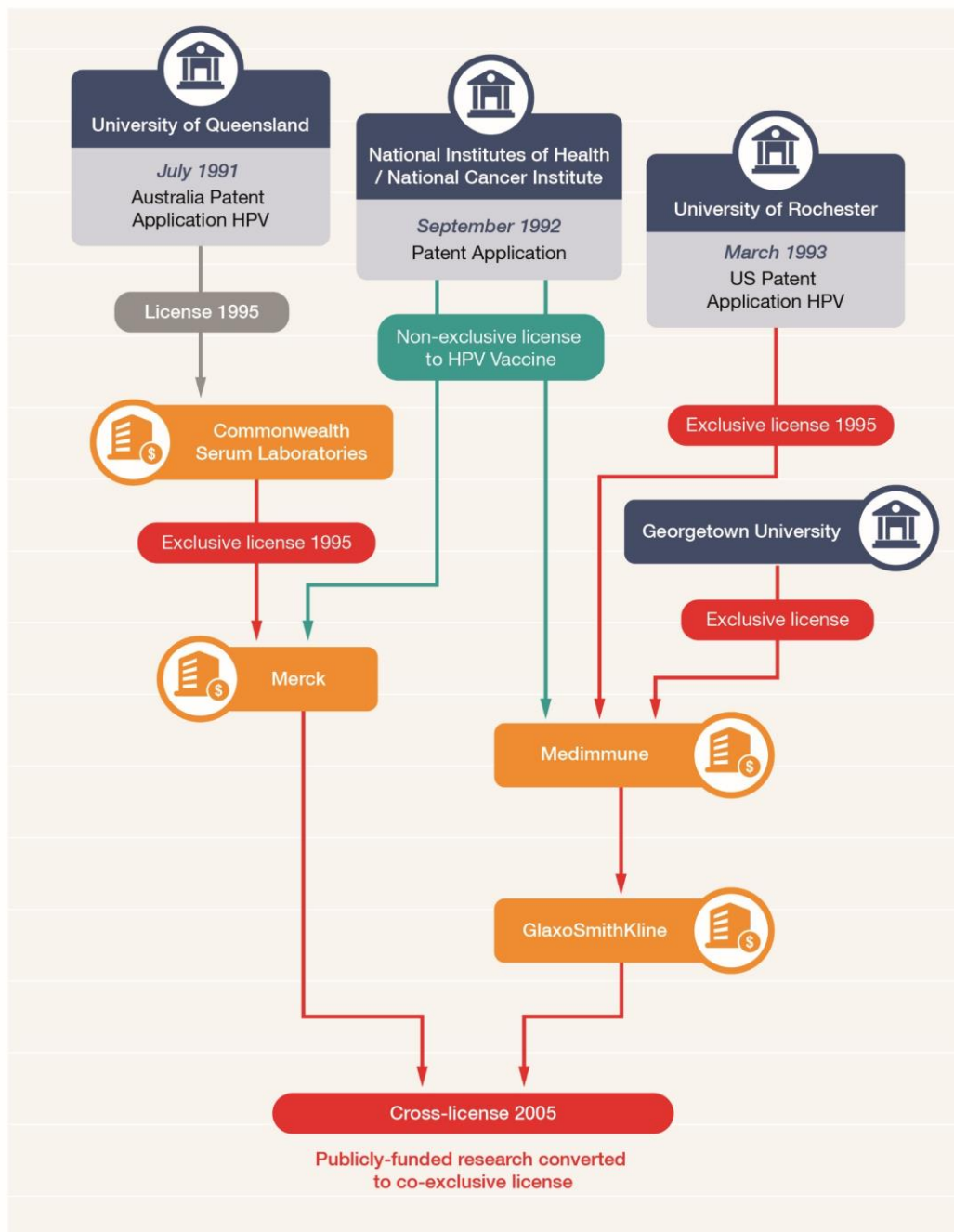
At the time of these activities, the US had a ‘first to invent’ system. Inventorship contests (or ‘patent interference proceedings’) were triggered at the U.S. Patent and Trademark Office by different patent applications filed by four different groups of inventors (those at Queensland, NCI, Georgetown and Rochester). Six different, two-way inventorship contests between the four parties continued for nearly a decade, with significant complexities and likely at significant cost to the parties.

Given all the uncertainty surrounding the ownership of this enabling HPV vaccine technology, and the possibility of mutually blocking exclusive rights if neither firm could be sure its products would not infringe on patent rights held by the other, Merck and GSK cross-licensed their respective IP holdings to each other in 2005 to ensure unrestricted mutual access to these HPV-related technologies. The patents under question expire between 2016 and 2028.

As part of the financial settlement of the patent interferences among the four original entities, the non-exclusive licences awarded by NCI and NIH to MedImmune and Merck were converted to co-exclusive licences, thus allowing both GSK and Merck access to this original IP and excluding any other potential competitors. Merck

brought Gardasil to the market in the United States in 2006 and GSK's Cervarix was introduced in the United Kingdom in June 2008.⁴⁸

Figure 2:
Cross-licensing of HPV Vaccine Patents



Public Institutions



Private Companies

Exclusive license

Non-exclusive license

Designing around the necessary technology

A second strategy available to potential manufacturers faced with patent barriers on vaccine technologies is to design alternate technologies to produce the vaccine, lessening or eliminating the risk of patent infringement. However, it is possible that an existing patent could cover a method or process for which there is no suitable alternative, in which case even the best R&D team cannot design around it. For instance, a patent on the gene sequence for HPV16 prevents potential competitors from using any antigen in any form in countries where the patent is granted, and a design-around strategy is not possible.⁴⁹

In designing around, companies may create their own approaches to dealing with various vaccine process steps, such as purification methods, yield improvement, formulations, adjuvants, dose reductions, analytical methods, antigens and delivery methods, providing the opportunity to potentially improve upon or create more cost-effective technology. It can take many years to design around patented technology, if possible at all. A key step in the process is a legal assessment that a company's new design does not infringe other IP or require licensing of any relevant technology.

Benefits and limitations

Some potential competitor vaccine manufacturers may find that designing around patent-protected processes of making vaccines is preferable, if they have the in-house ability to do so, because it can provide a greater level of freedom to determine and implement their own strategies, rather than be bound by licences that dictate terms. For some of the companies interviewed, their primary strategy is to work around competitors' patents.

One interviewed company felt confident in their 'design around' approach for a recombinant HPV vaccine targeting HPV 16 and 18, now in Phase III clinical trials. The overall IP landscape for HPV technology does not present a barrier for them because their cellular 'factory' for HPV 16/18 is based on the bacterium *E. coli*⁵⁰, which is different from other host cells.

However, in some cases the success of design around depends on the scope of the patent claims of a given technology. For example, for one interviewed company, designing around the technology disclosed in a GSK patent application on the HPV vaccine⁵¹, concerning a method of using a 'two dose regimen' HPV16/18 vaccine, has already taken two and a half years and may still fail because GSK's patent application claims are overly broad. Strict substantive patent examination practices and robust patent opposition procedures can support a successful design around strategy as some of the broad claims could be challenged and rejected, improving freedom to operate for a design around process.

Other limitations of this approach are that it requires a highly skilled technical team and sufficient resource support to design around existing vaccine technology successfully and can take a significant amount of time. As the success of a design around can sometimes be affected by non-technological factors, such as broad claims of the competitors' patents, simultaneous use of other strategies like challenging the patent may need to be considered. Additionally, there is always a risk of a 'design around' failing.

Challenging patents for the necessary technology

A third option available to potential competitor manufacturers facing patent barriers is to challenge a weak patent or patent application through a patent opposition or patent revocation process.

In this strategy, third parties can explain to a national patent office or other authority why a technology submitted for patenting is not eligible or patentable under national criteria. If the challenge is successful, the national

¹ The protein component of recombinant vaccines is often produced in *E. Coli* or yeast.

authority refuses the application or revokes the granted patent, eliminating it as a barrier to competition in that country.

Mechanisms to oppose patents, where available at all, vary procedurally from country to country. Different types of procedures also provide possibilities for third-party engagement; some being more formal than others. The length of patent opposition procedures varies among different jurisdictions; some can take up to three years or more.

Ways to challenge a patent can include: formal patent oppositions, less formal submission processes and other administrative or legal procedures. In a formal proceeding of pre- and post-grant oppositions, the patent office will engage with a third party (company, civil society or any other person) about their submission and the parties may be entitled to a hearing to further present the opposition. Challenging granted patents can also be accomplished through other administrative or judicial procedures, including but not limited to: patent invalidation, revocation and nullification. Some of these procedures are dealt with by patent re-examination boards or boards of appeal of the patent offices, and some are handled by the courts, depending on the specific provisions of the national laws.

Outside of formal patent opposition proceedings, some countries offer more limited opportunities for companies or civil society to provide information during a patent examination. For example, both Brazil and China accept third-party comments for the consideration of the patent office in the pre-grant phase, and these less formal procedures can still be, and have been, used effectively to challenge pending patent applications.

When opposing a patent, stakeholders can refer to the decisions of other countries as references; however, decisions to grant or refuse a patent application fall to national authorities. A revocation or refusal of a patent in one country does not mean it will be refused in another. For example, GSK has a broad patent in China for its HPV vaccine⁵² that may be of a concern for competition, yet the same patent application⁵³ was refused in Europe because it did not meet Europe's patentability standards. The patent may in fact also be invalid under Chinese patent law, if it were scrutinised.

Benefits and limitations

One benefit of the patent opposition approach is that if successful, competitor vaccine manufacturers have clearance to manufacture with a high level of autonomy and freedom to operate. Based on interviews, it appears that companies with patent opposition expertise and experience from other product areas, such as pharmaceuticals, are more likely to favour the use of oppositions. In countries that have robust patent opposition procedures allowing for in-depth third-party engagement, the likelihood of success for patent oppositions may be improved.

The limitations of this approach are that it can be risky, costly, lengthy and time-consuming. It requires a firm understanding of legal strategy and a skilled legal team or external counsel. Less formal opposition procedures, such as in Brazil or China, may not require mandatory feedback to the opponent nor for a hearing to be held by the patent office. It can be difficult for opponents to understand how the arguments they presented have been assessed by the patent office. A risk of this approach is that a negative outcome may significantly derail the development programme of a potential competitor, or compel it to continue with further judicial proceedings.

Case study: MSF and PCV patent oppositions

In March 2016, MSF filed a pre-grant patent opposition in India to block pharmaceutical company Pfizer from patenting a PCV13 composition (equivalent to PCV product claims).⁵⁴ This was the first time that a vaccine patent application had been challenged in India by a medical organisation. If successful, it was hoped that the opposition would help ensure more affordable versions of this lifesaving vaccine that could be made available to developing countries and humanitarian organisations. However, the pre-grant opposition was dismissed and

the patent was granted in August 2017. MSF is considering further action using other avenues available to address the barrier presented by this unwarranted patent.

Pfizer's patent application claims that the method of conjugating serotypes of streptococcus pneumoniae into a single carrier is new, but as MSF's pre-grant opposition asserted, this method is too obvious to deserve a patent under India's law. The application claims for using this old method to conjugate a wide range of serotypes could potentially block not only PCV13 production, but also vaccine production concerning any serotype(s) covered by the claims. A patent with such a broad claim could effectively dominate the technology and the market for PCV13 in those countries where the patent is granted. Pfizer's unmerited patent application on the PCV13 vaccine should have been rejected in India to open the door to more affordable versions of the vaccine being produced.

Outside of India, applications for this key patent⁵⁵ have been filed in many countries, for instance Australia, Brazil, Israel, Japan, Mexico, Spain and Slovenia. It has been granted in countries such as China⁵⁶, the Philippines^j, South Africa⁵⁷ and the US^k, and will expire between 2025 and 2027. In the US, a recent *inter partes* review (IPR) and post-grant opposition or 'post-grant review (PGR)' has been filed on this application.^l This application was granted and subsequently revoked by the European Patent Office (EPO) following opposition by other major pharmaceutical companies. An appeal by Pfizer is underway in Europe.⁵⁸

This patent is also under dispute in South Korea. The patent application⁵⁹ was initially refused by the patent office in 2012. It was subsequently granted after Pfizer amended the claims and resubmitted in 2013. A local competitor launched an invalidation procedure in 2013, followed by a revocation lawsuit, which is currently ongoing.^m Pfizer has also filed several divisional patents⁶⁰, based on the primary filing, intending to secure its market monopoly.⁶¹ The dispute in South Korea is particularly significant because a local firm has a follow-on alternative PCV13 product in an advanced stage of development. The current patent dispute could determine whether the local competitor can launch their version of PCV.

MSF has filed an 'amicus curiae brief' in support of the patent opposition in South Korea. In this brief, MSF emphasised "the global public health significance of pneumonia as the leading cause of childhood mortality and the critical impact of the concerned patent on hindering competition from Korean manufacturers in the pneumonia vaccine market," while calling for key claims to be rejected on the grounds that they do not meet the criteria required for granting a patent.⁶²

Strategies to improve national and international laws and policies

For all approaches available to potential competitor vaccine manufacturers for addressing patent barriers, governments can also play a role in creating an enabling framework within which competition is promoted. Governments can do this by setting strict standards of patentability, creating opportunities to oppose weak or unwarranted patents and establishing other mechanisms to protect affordable access.

TRIPS flexibilities and patent law

Countries can and should enforce limits on IP rules to help mitigate the negative effects of patents on the production and use of affordable vaccines. As recommended in the UN Secretary-General's High Level Panel

^j See PH12007502218 and PH12011502555.

^k See e.g., US7955605, US7709001, US8603484, US8808708, US8895024, US8895724, US9399060, US9480736 - all emanating from the same priority application

^l See Trial number IPR2017-01194 on US8895024; Trial numbers IPR2017-01211, IPR2017-01223, IPR2017-01215, PGR2017-00017, PGR2017-00016 on US9399060, available to search from USPTO Patent Trial and Appeal Board (PTAB) Bulk Data: <https://ptabdataui.uspto.gov/#/trials>

^m The full timetable of the events is available under the records on the primary patent KR 1020077025884 at Korea Intellectual Property Rights Information Service, available at: <http://eng.kipris.or.kr>

on Access to Medicines report, use of pro-public health IP rules in various countries and public health safeguards in the TRIPS Agreement can enable developing country research, development and production of more affordable medical technologies, including PCV and HPV vaccines. Specifically, countries should set strict patentability standards to ensure patents are only granted in appropriate cases and allow for oppositions against patents and patent applications that are unmerited, taking full account of the impact of patent provisions on the affordability and accessibility of new vaccines.

Set strict standards of patentability

Exclude patenting on specific dosages

Under the TRIPS Agreement, countries are not required to grant patents on methods of treatment, including dose regimens, yet many countries do. Patents related to dose regimens are often used in a patent ‘evergreening’ strategy, whereby companies seek multiple patents on the same product to prolong their market monopoly. These patents could negatively affect clinical practice and administration of lifesaving vaccines, in addition to prolonging monopolies and hindering competition.

For example, a patent application filed by GSK⁶³ attempts to protect a PCV10 product, containing various pneumonia-related antigens, for which the dose is given between three different ranges (1 and 10 µg, 1 and 5 µg or 1 and 3 µg). If the distinguishing feature of a patent claim is only the dose regimen, the claim should not be patentable. Excluding dose regimen patents is an ethical and public health concern. Clinicians should not be restricted in applying their best skill and judgment for fear of infringing a patent covering a form of medical treatment.

Countries should instead apply rules limiting abusive evergreening practices and avoiding additional monopoly protection for different dose regimens of a known vaccine without sufficient technical advancements and merits for people’s health. Laws and regulations of this nature in Indiaⁿ and Argentina⁶⁴ set up strict scrutiny practices, and claims on insignificant changes of known substances do not deserve patent protection under these laws. These rules could be used to refuse claims related to dose regimens and other secondary claims for patent protection.

In another approach, Brazil’s national patent law provides that its health regulatory agency, the National Sanitary Vigilance Agency (ANVISA), collaborates with the patent office in the examination of patent applications claiming pharmaceutical inventions, often referred to as ‘prior consent,’ to avoid the patenting of inventions that are merely minor modifications of existing products.⁶⁵ This type of procedure could also be used in other countries to scrutinise vaccine patent claims.

Exclude patenting on other diagnostic, therapeutic and surgical methods for treatment

The TRIPS Agreement enables countries to exclude “diagnostic, therapeutic and surgical methods for the treatment of humans or animals”^o from patent eligibility criteria. Countries that exclude these methods from eligibility criteria are better able to prevent excessive patenting practices by originator companies, such as efforts to patent methods of use and treatment. For example, as noted in this report, GSK has a patent application directed to the method of administering ‘two-dose regimen’ HPV vaccines⁶⁶, and a South African patent⁶⁷ on the method of immunising patients with PCV.

Excluding patenting on methods of treatment has critical public health and ethical significance. This type of claim has been excluded from patent eligibility in many national laws, such as those under the Patent

ⁿ Section 3(d) of India Patent Act.

^o Article 27.3(a) of TRIPS Agreement.

Examination Guidelines of Argentina, Article 10.VIII of the Brazil Industry Property Law, Article 25 (3) of the China Patent Law and Section 3(i) of the India Patent Act.

In India, a critical safeguard is also provided under Section 3(d) of India Patent Act, which states that the “mere use of a known process, machine or apparatus [is not patentable] unless such known process [machine or apparatus...] results in a new product or employs at least one new reactant.” These provisions should be used to challenge or refuse patent applications that contain claims which have low technological contribution but high commercial and strategic importance, such as those covering a broad range of antigens or treatment regimens for specific age groups. It may be useful for particular countries to refer to ‘dosage claims’ as a ‘method of treatment’ so that these types of claims could be challenged under TRIPS.

Limit composition patents on vaccines

Patents on vaccine compositions are common. Once again, it is important for patent offices to make full use of the flexibilities available under TRIPS to set rigorous patentability criteria and examination practices, to provide the strict scrutiny necessary for subjects bearing great public interest, such as vaccines.

As described, MSF is attempting to invalidate a broad Pfizer patent application on PCV based on a lack of adequate technical disclosure and a lack of novelty and inventiveness; these are standard measures of patentability criteria. However, there are also other patentability criteria, fully legal under TRIPS, that can be better defined and applied.

For instance, India’s patent law Sec 3(e) states “a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance” is not patentable. Under the appropriate circumstances, this might help to refuse a vaccine composition (e.g., antigen, conjugate, adjuvant, preservative) as merely an ‘admixture.’ Similarly, the Argentina patent guidelines assert that “both formulations and compositions will be considered obvious...[and] exceptionally, claims directed to formulations will be acceptable when a long-felt need is solved in a non-obvious manner.”^{68,69}

These are two examples of criteria that might be used to limit broad composition patent claims on vaccines. The burden of proving that a vaccine composition solves a long-felt need in a ‘non-obvious’ manner should rest squarely on the shoulders of the vaccine company, especially if, as in the Pfizer situation above, a composition patent would introduce an absolute barrier where granted.

Strict patentability criteria safeguard public health, barring some unmerited patent applications from being granted in the first place. Adapting and using strict patentability criteria in patent examination practices requires countries to set clear policy and legislative goals of protecting access to affordable medical technologies and a skilful work force in patent offices.

Introduce or improve patent opposition options

Another measure countries can take to promote vaccine competition is to introduce and improve patent opposition options, allowing for additional oversight and safeguards against the granting of unwarranted patents that might unnecessarily block or delay competition.

Transparent pre- and post-grant opposition and revocation regulations, such as those under India’s legal system, allow any person, including potential competitor vaccine manufacturers and other entities such as civil society organisations, the opportunity to demonstrate why the patent office should refuse a patent application or revoke an issued patent, with the opportunity to have official hearings held by the patent office.

Introduce full TRIPS public health safeguards, including a patent opposition system, in South Africa

South Africa has a depository system of granting patents that does not include substantive search and examination on patent applications. It also does not currently have any mechanism for third parties to oppose

patent applications. South Africa does not make full use of TRIPS flexibilities to safeguard public health. As a result, the country has granted a substantial number of patents for medicines and vaccines, which might have been avoided if better criteria, examination and opposition procedures had been in place as safeguards.⁷⁰ During the current process of reforming South Africa's patent law, the introduction of substantive patent examination and patent opposition systems is critically needed, among other measures to fully introduce TRIPS flexibilities in the country to promote access to affordable medicines.⁷¹

Improve the patent opposition procedures in Brazil and China

At present, procedures to challenge patent applications and granted patents in Brazil and China include providing observations on the published pending patent applications and a patent invalidation procedure involving patent re-examination and judicial proceedings. The observation procedure under Article 31 of Brazilian Patent Law and Rule 48 of the Implementation Regulation of Chinese Patent Law allows any person to submit the observations to the patent office on a published patent application. It has been widely and successfully used as a critical way of opposing unmerited patent applications, including those concerning medicines. However, the patent examiner only takes these submissions as references and has no obligation to respond or hold a hearing. Thus, the public is not notified of the handling of comments, amendments or any other observations submitted during the course of this procedure. The rules in Brazil and China should be changed to afford the public the opportunity to view the submitted documents and observations and allow for public comment on these proceedings.^{72,73}

Improve and expand implementation of the Bolar exemption and remove provisions on patent 'linkage' in regulatory laws

Patent law, drug regulatory law and competition law intersect in many ways. Rules concerning patent 'linkage' require regulatory bodies to ask or verify whether a follow-on product registration is infringing any patents held by originator companies. This requirement goes beyond TRIPS obligations and asks regulatory bodies to enforce private patent rights, an improper mandate for a regulatory body that should be solely charged with determining the quality, safety and efficacy of medical products.

Patent linkage establishes an inappropriate relationship between product registration and patent protection and raises an additional barrier to the entrance of follow-on competitors into the market because it delays the onset of competition. It amounts to a de facto extension of a patent term. Countries such as China^P that have provisions on patent linkage in national drug regulatory laws should remove these requirements.

Patent linkage could dilute the effects of 'Bolar exemptions'. A Bolar exemption permits a third party to produce and use a vaccine under patent for purposes related to regulatory approval without risk of patent infringement charges. This exemption is protected under the TRIPS Agreement and serves as a public health safeguard. Application of such exemptions could enable interested vaccine manufacturers to conduct PCV and HPV vaccine development and initiate clinical trial and regulatory approval processes as early as possible without being at risk of patent infringement. This could help ensure a timely entry of competitors' follow-on products and improve affordable access to vaccines. Some countries, such as Brazil, China and India, already have

^P Article 18 of the Chinese Food and Drug Administration (CFDA)'s Registration regulations states that an applicant for market registration must provide patent information "in respect of the drug applied for registration, its formula, manufacturing processes and/or uses." If the applicant is not the patent holder in China, the applicant (in this case a DCVM) must "provide a statement of non-infringement." This requirement of submission of a non-infringement statement by the applicant places an unnecessary burden on the applicant and, perhaps even more importantly, it is beyond the CFDA's mandate and competency to review such non-infringement statements.

provisions on Bolar exemptions that are applicable immediately. This allows preparation for the entry of a competitor before the relevant patents expire, enabling regulatory bodies to accept and review applications on follow-on products any time during the relevant patent term.⁹ In other countries, this exemption only applies two years before patent expiration. Countries should introduce or expand Bolar exemptions in their regulatory laws to accelerate the introduction of competition.

Improve rules and ease of use regarding compulsory licences

Other TRIPS public health safeguards include the ability to issue compulsory licences for public health interests and to suppress anti-competitive practices. TRIPS allows countries to define a broad range of legal grounds upon which a compulsory licence can be pursued. These include, but are not limited to: when public health interest is at stake, when patent holders fail to fulfil obligations to use the patent in the country, when negotiation for a voluntary licence fails to reach a conclusion, when the existing patent would block follow-on invention activities or when the behaviour of using patents amounts to anti-competitive conduct, such as setting high prices that prevent competition and access. The use of compulsory licences has proven to be an effective way of overcoming patent barriers to access critical health products and could also be employed as a threat by governments in their price negotiations.

Improve practice and transparency of licensing

Vaccine IP licensing language negotiated with fewer restrictions on geographic coverage, fairer royalty payments, the ability of licensees to challenge the licensor's patents, fairer grant-back conditions and other terms, such as termination clauses, could improve outcomes for licensee vaccine manufacturers. Unfortunately, conventional contract language typically does not consider access challenges and does not ensure product affordability or accessibility. For example, clauses asking for exclusive production by using only the licensor's technology and marketing on behalf of the licensor in certain countries could crowd out all other competitors and keep in place the de facto monopoly of the patent holder. When leaving control entirely to monopoly-holding companies, even the lowest prices they offer in the marketplace may not be affordable. Explicit stipulation of prices in such agreements may also raise antitrust issues.

When using licensing as one of the strategies to address monopoly barriers for vaccine manufacturing, companies (both licensors and licensees) could improve licensing practices by adapting non-exclusive licensing and including explicit obligations for both licensor and licensee to ensure access and affordability. A contract can also create a 'non-suit' or 'non-assertion' agreement, which, in effect, bars the holder of the IP from enforcing the IP within a certain set of countries and under a certain set of conditions.

It is challenging to provide a detailed critical analysis of in-licensing options because most licences and technology transfer agreements are negotiated and executed in secret. Presently, licensing agreements remain largely a commercially confidential practice, even though they deal with the transaction of IP, a subject that carries significant public interest yet minimal possibility for public involvement. There are no databases or other publicly available sources where signed licences are maintained. There is also little information about best practices of regulating licensing and technology transfer agreements by national governmental authorities, wherein transparency could be ensured. An information database should be created, and all signed licences and agreements, together with key IP information, on medical products and tools should be published for public scrutiny.

⁹ Article 19 of the Chinese medicines registration law originally required the Chinese medicines regulatory authority (CFDA) to (i) accept registration filings by generic companies two years before expiration of the relevant patents of the innovative drug, and (ii) issue market approvals to generic manufacturers only after the relevant patents expire. Recently, this two-year window for generic filings was eliminated.

Conclusion and recommendations

When potential competitor vaccine manufacturers want to produce vaccines for which there are patent barriers affecting relevant technology, there are a number of options to address these barriers. These options may be used alone or in combination, but each comes with its own challenges and considerations. Similarly, there are many steps that countries can take to contribute to price-lowering competition.

Countries, companies, international organisations responsible for health and intellectual property and donors can all support efforts to help promote competition and to mitigate the threat of patents on access to affordable vaccines.

Countries

Countries can take a variety of steps to promote competition in vaccine manufacturing and help mitigate the complex patent thickets that could block, delay or increase uncertainties around access to multiple sources of vaccines. Governments should adopt public health-oriented IP policies, making the full use of TRIPS flexibilities in both substantive and procedural aspects in national patent laws.

- **Encourage and accelerate** follow-on development and competition of vaccines and vaccine technologies through the introduction and use of broad Bolar exemptions to support an early start of research and clinical studies by follow-on manufacturers, and support independent follow-on research and development.
- **Apply strict patentability criteria** for vaccine and vaccine technologies in patent examination and judicial proceedings. Countries should closely scrutinise patent applications concerning common methods of treatment, dosage forms and claims concerning specific age groups. Countries should reject trivial changes to known vaccine technologies, or composition patent applications that merely present the assembly of more ingredients using a known technology.
- **Implement robust pre- and post-grant opposition procedures** in national patent law systems that allow greater public scrutiny and opportunities to challenge unmerited patent applications from an early stage. Procedures that allow third-party observation but lack a mandatory hearing requirement could be improved to provide better transparency and accountability to the public.
- **Improve use of compulsory licencing.** Governments should also strengthen the mechanisms of issuing compulsory licences to facilitate the most expedited access to multiple sources of vaccines and to safeguard public health.
- **Strengthen technical capacity** to ensure patent examiners apply strict patentability criteria and screen out unmerited applications in a timely manner. This will provide clarity on the patent landscape concerning important vaccines and technologies.
- **Increase transparency** of patent office filings to enable third parties to better understand the IP landscape, especially through procedures to promote disclosure of non-proprietary biological qualifier names⁷⁴ of vaccines. Prospective manufacturers will be able to make decisions more efficiently if they understand the IP landscape clearly, and government procurement decision making will also be improved by addressing the current information asymmetry.
- **Make full use of LDCs exemption** for patent protection to accelerate access to quality assured follow-on new vaccines and encourage competition to improve affordability of vaccines.
- **Demand that international organisations** like WHO, Gavi, the Pan American Health Organization (PAHO) and the United Nations Children's Fund (UNICEF), improve technical

support for countries to: identify legal barriers, use flexibilities under intellectual property laws and improve transparency of patent information to facilitate follow-on development and foster robust competition for new vaccines.⁷⁵

Companies

To ensure that patents do not restrict access to affordable vaccines, patent-holding companies should commit to:

- **Transparency on price** information of new vaccines.
- **Transparency on the IP landscape** of vaccines.
- **Refrain from applying evergreening strategies**, particularly through filing unmerited or abusive patents and numerous additional patent applications on old technologies.
- **Implement access strategies**, including affordable pricing and appropriate licensing terms, for licensee manufacturers to enable widespread access and competition. This includes signing licensing agreements that do not lead to excessive royalty payments, that are transparently published and that provide licensees with freedom to operate in a broad geography of countries.
- **Include all technologies and know-how** needed by licensees in the context of technology transfer without any restrictive conditions and provide sufficient assistance for licensees to access a third party's technologies needed for vaccine development.

Competitor manufacturers should also commit to transparency, explore and strengthen capacity for design-around approaches, make full use of available legal channels to challenge patents that restrict their freedom to operate and refrain from signing restrictive licences that block competition, while also refraining from filing additional patent applications themselves that limit both R&D and competition.

All companies should support the use of TRIPS flexibilities as a commitment to improve access to affordable new vaccines. This includes increasing understanding of the TRIPS LDC exemption, and accelerating supply of new vaccines at affordable prices in LDC countries.

Multilateral Organisations (UN, WHO, WIPO, UNICEF)

Multilateral organisations can take a number of actions to support countries in their efforts to promote access to affordable vaccines. Specific examples include:

- **Provide information and technical support** including: publishing patent landscape reports and analyses; issuing guidelines of public health approaches to patentability criteria and patent examination for vaccine technologies; offering technical assistance to governments concerning the impact of patents on follow-on development, competition and access to affordable new vaccines; and supporting the use of appropriate legal and policy measures to mitigate the negative implications of patents.
- The World Intellectual Property Organization (WIPO), which has published general, descriptive patent landscapes⁷⁶ on PCV, rotavirus vaccine and vaccines for infectious diseases, should revise its landscape reports to be specific and practical, as well as analyse the implications of the patents that they have identified for competition.
- WHO, in fulfilling its mandate under WHA Resolution 61.21 of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property and WHA Resolution 68.6 of the

Global Vaccine Action Plan, should provide adequate technical support to governments to improve and use legal measures, including reform of patent laws where appropriate.

- WHO should also publish an analysis of the impact of patents on affordable access to new vaccines, as well as guidelines and recommendations for public health-oriented patentability criteria and examination of new vaccine technologies.
- UNICEF, in furthering its commitment to transparency and accountability, and with its Supply Division that is responsible for procuring vaccines for Gavi and other developing countries (spending over US\$ 1.7 billion in 2015), should identify patent barriers for vaccines that it purchases and address these barriers in collaboration with governments, civil society and other appropriate multilateral institutions, in particular WHO.
- **Promote a global vaccine price monitoring mechanism** to improve transparency and facilitate procurement practices in developing countries, particularly WHO's V3P database, which improves transparency and equips governments with price data that improves their ability to negotiate affordable access to vaccines.
- **Strengthen national authority capacity to critically review patents.** As recommended by the report of the United Nations Secretary-General's High Level Panel on Access to Medicines, WIPO should work with other multinational organisations to provide capacity building to national patent offices and examiners in developing countries on application of strict patentability criteria, considering the impact on public health.⁷⁷

Gavi, the Vaccine Alliance

For countries that are excluded or have 'graduated' from Gavi support, the impact of patenting activity and monopoly barriers on access to new vaccines contributes to financial difficulties. Gavi should address these issues as an integral part of its financial support, market shaping work and procurement policies. Gavi should:

- **Encourage, accelerate and support competition** of vaccines and vaccine technology development by facilitating measures to overcome patent barriers and regulatory constraints for follow-on vaccine manufacturers.
- **Increase its market shaping activity** through investment in stimulating competition by addressing IP barriers in its Supply and Procurement Strategy.
- **Provide information and technical support** to both potential new suppliers and national governments concerning the legal and policy options in overcoming patent and regulatory barriers to access more affordable vaccines.
- **Regularly publish key patent information**, in collaboration with WHO, concerning priority vaccines.

Funders and Donors

Funders and donors to vaccine development as well as immunisation programmes in developing countries determine how their resources are used and therefore have significant influence to improve competition and vaccine affordability. Funders and donors should:

- **Set clear access principles** in grant and funding policies that are transparently published. For example, the Bill and Melinda Gates Foundation, a leading funder of vaccine development for products that target the health needs of developing countries, should set broad, transparent access

principles that ensure affordable access to new vaccines for all low- and middle-income countries at one affordable, low price.

- **Improve the assistance and information services** on IP barriers and strategies for beneficiary countries.
- **Provide technical assistance** to countries in improving the use of TRIPS flexibilities, to address the challenges of lacking competition and high prices of new vaccines.
- **Promote the use of public health exceptions** allowed by IP laws to facilitate public procurement and non-commercial use of vaccine products.

ANNEX 1: Sample Questions Used in Semi-Structured Interviews

General questions on IP management:

We would be interested in the general governance structure of IP management:

1. How many people/departments are working on or getting involved in IP works?
2. Who is doing what and the collaboration mechanism if any?
3. The overall annual budget for IP related work
4. Is your IP work (patent searching, analysis and FTO reports) done in-house and/or outsourced?

Questions on specific IP portfolio management and licensing:

1. What is your overall strategy of acquiring technologies for domestic vaccine development? Do you acquire through in-house R&D work-around, collaboration with domestic research institutions, and collaboration with institutions overseas, through technology transfer agreement with others, in-licensing from other companies or others?
2. Do you acquire technologies from international or foreign public institutions such as WHO and NIH? On what subject?
3. When you choose one of the above or other strategies of acquiring needed technologies, what are the key factors of consideration that will be taken into account?
4. With regard to domestic market, are you acquiring or in-licensing any of the IP relating to your overall business strategy for these vaccines?

If YES, which IP are you in-licensing and why?

- How much time and money has been spent on acquiring a licence to these vaccines?
- What are the facilitating factors/enablers to acquiring the IP relating to your overall domestic business strategy?

If NO, why not?

- Is this because your company has developed their own IP?
- Which IP has your company developed and why?
- How much time/effort/FTE has this 'cost' your company?

5. What are barriers to acquiring the IP relating to your overall domestic business strategy for these vaccines?
6. With regard to your overseas/international markets, are you acquiring or in-licensing all of the IP relating to your overall business strategy for these vaccines? (SAME SERIES OF QUESTIONS AS ABOVE)
7. Is your IP strategy for HPV and/or PCV geared to:
 - Broader coverage vs. taking what you can get (i.e., narrow coverage)
 - Is your strategy geared more to (cross-) licence than in- or out-licensing?
 - Would you oppose a patent or litigate domestically or other markets to support your priority HPV and/or PCV and/or rotavirus IP?

If YES, why?

If NO, why not?

8. How much would it 'cost' your company to oppose and/or litigate a patent? How much money and time? How many FTEs? Do you have specific examples?
9. What are the facilitating factors/enablers to your opposing patents and/or litigating patents to HPV and PCV domestically? In other countries?

10. Has your company ever:

- Published results or details as a defensive posture to prevent others from patenting HPV and/or PCV and/or rotavirus?
- Decided not to file patent applications relating to HPV and/or PCV and/or rotavirus?

Questions related to ‘blocking’ patents and know-how:

In your general practices, could you tell which of the below categories would most likely pose ‘blockage’ or ‘delay’ in your development and production? Any other types of IP that you have more concerns?

“Blocking IP” related to biological materials (please provide examples of each, if applicable):

- Vectors
- DNA sequences
- Viral particles
- Cell lines,
- Monoclonal antibodies
- Others

“Blocking IP” related to process/devices (please provide examples of each, if applicable):

- Assays for detection of virus
- Assays for immunogenicity
- Specific culture conditions
- Specific conjugate chemistry
- Purification process
- Adjuvant(s)
- Thermo-stability procedures
- Dosages
- Treatment regimens
- Injection devices
- Others

Concluding questions:

1. Is the IP system ‘working’ to allow you to produce vaccines that are affordable and accessible?
2. Does the current national IP law and policy create barriers to acquiring the IP relating to your overall domestic vaccine strategy?
3. What are the facilitating factors/enablers to acquiring the IP relating to your overall international vaccine strategy? And likewise, what are the hindrances?
4. How would you suggest to improve IP law? For example, what type of patentability criteria may be more beneficial in developing your own vaccines, whether the patent opposition/revocation procedures can be used and improved for the purpose of supporting vaccine follow-on development?
5. Any other suggestions on law and policy framework that you think would be beneficial to accelerate follow-on development and competition?

Title	Multivalent Pneumococcal Polysaccharide-Protein Conjugate Composition	15-Valent Pneumococcal Polysaccharide Protein Conjugate Vaccine Composition	Separation of Contaminants from Streptococcus Pneumoniae Polysaccharide by pH Manipulation	Vaccines Containing Aluminium Adjuvants and Histidine	Conjugate Vaccine	Streptococcus Pneumoniae Vaccine Formulations
Patent Application Pending In	Brazil India (Opposed by MSF and Panacea)	China India (Opposed by Panacea) Thailand	Brazil India	Brazil		China India (Opposed by Panacea)
Patent Application Filed In	Australia (Published) Chile Israel Jordan (Status unknown) Kosovo Thailand (Status unknown) Venezuela	Australia (Published) Brazil (Status unknown) EPO (Published) Philippines (Status unknown) Ukraine (Published)	Australia (Published) EPO (Published) Israel (Pending) Mexico (Pending) Philippines (Status unknown)	Japan (Pending) Mexico (Pending) USA (Pending)	Egypt Mexico Philippines (Status unknown) USA (Published)	Brazil (Status unknown) USA (Pending) EPO (Pending) Australia (Pending) Canada (Pending) Israel (Pending) Japan (Pending) South Korea (Pending) Mexico (Pending) Russia (Pending)
Patent Application Withdrawn	Germany Russia		Germany Russia		Australia China EPO Germany South Korea India (Following pre-grant opposition by Panacea)	
Other Status	EPO (Under revocation procedure) South Korea (Under invalidation procedure)				Brazil (Lapsed)	

Abbreviations

ANVISA	Agência Nacional de Vigilância Sanitária (Brazil)
DCVM	Developing country vaccine manufacturer
EPO	European Patent Office
FTO	Freedom to operate
GSK	GlaxoSmithKline
HPV	Human papillomavirus
IP	Intellectual property
INPI	Instituto Nacional de Propriedade Industrial (Brazil)
LDC	Least-developed country
MSF	Médecins Sans Frontières
NCI	National Cancer Institute
NIH	US National Institutes of Health
PAHO	Pan American Health Organization
PCT	Patent Cooperation Treaty
PCV	Pneumococcal conjugate vaccine
R&D	Research and development
SIPO	State Intellectual Property Office (People's Republic of China)
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
UNICEF	United Nations Children's Fund
VLP	Virus-like particle
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Glossary

A Fair Shot: A global campaign launched by MSF in 2015 to urge Pfizer and GlaxoSmithKline to drop the price of their pneumococcal conjugate vaccines to US\$5/child for developing countries and humanitarian organisations.

Adjuvant: A substance added to a vaccine to boost the generated immune response, providing a higher antibody titre, and therefore, longer-lasting protection. Adjuvants can also gear the immune response to particular types of immune cells, which further improves the efficacy of the vaccine.

Amicus curiae brief: A brief filed by someone with a strong interest in the subject matter of a lawsuit, but who is not a party to nor directly involved with the litigation.

Antigen: A substance that is recognised by antibodies and immune cells to generate an immune response.

Blocking patent: A patent that prevents another parties from making or using the patented technology without infringement, because it relies on the invention covered by the first.

Bolar exemption: A legal provision that allows a medical product under patent to be produced and registered by a competitor manufacturer without the risk of patent infringement charges.

Cold chain: A global network of equipment and services to ensure that vaccines and medicines stay at the right temperature at every step of their journey.

Compulsory license: A compulsory license is an authorisation by a competent government authority for a third party, or the government itself, to make use of the patented subject matter without the consent of the patent holder.

Cross-license: The licensing of exclusive intellectual property holdings between two patent holders, to provide unrestricted mutual access to previously mutually blocking exclusive rights, to the benefit of both parties.

Divisional patent: A type of patent that contains matter from a previously filed application.

DNA sequence: DNA, which is short for deoxyribonucleic acid, is a molecule that provides the genetic code of all organisms. Four different forms of the molecule, combined into a code, ensures that each organism has a unique genome. Segments of an organism's DNA encode specific proteins that fulfil functions in the cell and body.

E. coli: *Escherichia coli* is a bacterium that is commonly found in the lower intestine of warm-blooded organisms. Most serotypes are harmless, although some can cause gastrointestinal irritation, colitis and diarrhoea. *E. coli* cells are popular host cells for recombinant viral products, due to their ease of use and low cost. *E. coli* cells, transfected with viral DNA or RNA, are an example of virus-like particles.

Evergreening: A strategy that involves the filing of numerous additional patent applications to extend the monopoly on a certain product and delay competition.

Excipient: An inert, natural or synthetic, substance that serves as a medium to convey the active ingredient.

Expression vector: An artificial construct used to introduce a specific DNA sequence into a target or "host" cell. The target cell's intrinsic protein synthesis mechanism produces the protein, such as an antigen, encoded by the DNA sequence.

Gavi: Gavi, the Vaccine Alliance is a public-private global health partnership with the objective of increasing access to immunisation in poor countries.

Grant-back conditions: A requirement often included in a voluntary license, by a licensor that any improvement made during the licensing period to whatever was licensed to the licensee, must be told and given

to the licensor. Some grant-back clause in license agreement may cause anti-competitive concern when it makes the positions between licensor and licensee significantly unequal.

HPV 16/18: A vaccine to provide immunity to types 16 and 18 of human papillomavirus, which together account for over 70% of cervical cancer cases.

Inter partes review: a trial proceeding brought by third party and conducted at the Patent Trial and Appeal Board of the United States to review the patentability of one or more claims in a patent concerning novelty and obviousness. Source: United States Patent and Trademark Office, Patent Trial and Appeal Board, 2014.

Multi-dose vial: A vial of medication intended for parenteral administration (injection or infusion) that contains more than one dose of medication.

Non-suit or Non-assertion agreement: Non-suit or non-assertion, or covenant not to sue, refers to the type of agreement reached with the patent holder that certain patents will not be enforced by the patent holder under the defined conditions. This can be reached under a license agreement or a separate agreement between licensor and licensee.

Non-proprietary biological qualifier name: The name of a biological medicine that is not subject to trademark rights and is recognised across the industry. Non-proprietary names allow communication to be more precise by providing a unique standard name.

Patent: A patent is the right to prevent anyone else from making, using, selling or offering to sell the patented invention. A patent is granted by a government or regional authority. The patent term usually lasts for 20 years, which means that during this period of time, the patent holder has a monopoly on the invention (e.g. a medicine) and can charge the highest price the market will bear.

Despite procedural collaboration among member states of the Patent Cooperation Treaty (PCT) system under the auspices of World Intellectual Property Organization (WIPO), patent law is territorial and patents are granted on a country-by-country basis. The same patent application could be granted in one country and rejected in another. Least-developed Countries (LDC) have no obligation to provide patent protection in general until 2021, and on medicines (including vaccines) specifically until 2033.

Patent claim: Patent claims are the part of the patent application where the inventor defines the legal scope of a patent and what will be protected by patent law.

Patent landscape: A patent landscape provides information of the patent situation around a particular technology or product (e.g. vaccine) in a country or multiple countries. It often includes the identified key blocking patents, legal status and summary of the scope of the protection those patents entail.

Patent linkage: The unnecessary relationship between the registration of a product and the patent protection of the same product that provides an additional hurdle to the entry of competitors into the market and informally extends the monopoly.

Patent opposition: An administrative procedure available under intellectual property law of many jurisdictions that allows third parties to challenge the validity of a pending patent application (pre-grant opposition) or of a granted patent (post-grant opposition). The post-grant review procedure in the US is a similar procedure to post-grant opposition.

Patent thicket: An overlapping set of intellectual property rights that complicate the freedom to operation analysis, and inhibit or delay competitors.

PCV13: A pneumococcal conjugate vaccine that provides immunity to 13 serotypes of the pneumonia-causing bacterium, *Streptococcus pneumoniae*. The only available PCV13 is Pfizer's current version of the pneumococcal conjugate vaccine marketed as Prevnar13.

Polysaccharide: A polymeric carbohydrate molecule composed of a long chain, which can be linear or branched, of different sugar units bound together. Polysaccharides are commonly found on the cell surface and can also act as antigens.

Prior art: any evidence, in defined forms of disclosure or publication according to applicable law, that can prove a given invention is already known.

Reagent: A substance used in a chemical reaction.

Recombinant DNA: DNA that contains genes from different sources that have been combined by the techniques of genetic engineering rather than by breeding experiments. Genetic engineering is therefore also known as recombinant DNA technology. Source: Oxford Concise Colour Medical Dictionary, Third Edition, Oxford University Press 2003.

Research exception: A legal provision that exempt the research and experimental use of a patented subject matter from being held as infringement.

RNA sequence: RNA, which is short for ribonucleic acid, is a molecule that is used to create long chains that encode messages. It acts as an intermediate between DNA and protein synthesis.

Royalty payment: A payment made to the legal owner of a patent by those who wish to make ongoing use of the patent for their own purposes.

Serotype: A category into which material is placed based on its serological activity, particularly in terms of the antigens it contains or the antibodies that may be produced against it. Source: Oxford Concise Colour Medical Dictionary, Third Edition, Oxford University Press 2003.

Substantive patent examination: A process, in which a patent administrative authority would determine whether an application will be granted a patent protection, based on technical assessment and examination of the technical features of the application against the patentability criteria of the concerned jurisdiction.

Vaccine: A biological substance used to stimulate the development of antigen-specific humoral (antibody) and cellular immunity, and thus confer active immunity against a specific disease or number of diseases, produced by culturing bacteria or viruses under conditions that lead to loss of their virulence but not of their antigenic nature. Other vaccines consist of specially treated toxins or antigenic dead bacteria, or are live but attenuated organisms.

Vaccine valency: The valency of a vaccine describes the number of strains of a microorganism, or the number of microorganisms, that the vaccine provides immunity against.

Virus-like particle: Particles that resemble viruses but are non-infectious because they contain no viral genetic material, such as a self-assembled envelope proteins.

Voluntary license: A voluntary agreement reached between the patent-holder (licensor) and another party (licensee) (usually a generic company) which allows the licensee to make, use, and/or sell patented medicines. Terms and conditions can specify in which countries a medicine can be sold and what the royalty will be.

TRIPS Agreement: The TRIPS Agreement was signed in 1994, and entered into force in 1995. It is administered by WTO and provides minimum standards that protect IP rights that all its members must comply with, with exceptions for Least-Developed Countries members who do not have to implement TRIPS Agreement in general till 2021, and on pharmaceuticals till 2033. Several flexibilities within this agreement can be employed to act as public health safeguards. These flexibilities were expressly reaffirmed in the Doha Declaration on TRIPS and Public Health of 2001.

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