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Developing Drugs for Developing World Diseases: The Role of Patents

The Covid-19 pandemic has brought the issue of patents for medicines (in particular vaccines in the case of Covid) to the fore. From the debate surrounding enhancing distribution of Covid vaccines in the developing world by implementing a patent waiver, it is clear that the oft-heard argument that intellectual property to protect such vital products is inherently "a bad thing" is overly simplistic.

How can intellectual property best be used to ensure that the medical needs of those in developing countries are met?

Some argue that intellectual property and patents in particular are the root of all evil, and therefore the solution lies in getting rid of all patent protection. Others argue that patent protection is the answer and therefore that more and stronger patent protection will provide the solution. Pharmaceutical companies argue that if there is no patent protection then there would be no research and development for developing world diseases at all, and that tampering with the patent system could be counterproductive and illegitimate.

The truth probably lies somewhere between these extreme positions. Many of the problems of access to medicines exist *despite* intellectual property protection, not *because* of it. It is not necessarily a question of *whether* patents help, but *how* they can help.

Introduction to Patents

A patent is a time-limited monopoly granted to an inventor as a reward for innovation, and a patent may be granted for an invention that is new, inventive, and industrially applicable. In most cases, the monopoly is limited to 20 years from the filing date of the patent application. The owner of the patent right is, in the first instance, the inventor or, as is often the case, the inventor's employer. The patent owner benefits by being able to exclude others from exploiting the invention (without its permission) for those 20 years. This means that the patent owner can either exclusively manufacture or carry out the invention and therefore charge a premium

due to the lack of competition, or it can grant licences (which may be exclusive or otherwise) and earn an income through royalties.

Patents are territorial. This means that a patent must be applied for in every country in which protection is desired, though most applicants will seek protection in only the countries where it expects its major markets to be. This doesn't mean the patent owner cannot exploit its invention in other countries, but it does mean that it cannot stop others from doing so also.

An important point to note is that patents provide a "negative right". They allow the owner to prevent third parties from carrying out the invention without permission. Patents do not provide any "positive right". In other words, it is possible for a patent owner to hold a patent, but not be able lawfully to work the invention, for example, in view of earlier rights held by others.

One major misconception that many people have is that the patent system in some way encourages secrecy. In fact, the opposite is true. In order to obtain a patent, the invention must be described in the patent application in such a way that the so-called "skilled person" could follow the "instructions" in the patent application to carry out the invention. The skilled person is only allowed to add information within the common general knowledge in their technical field. Furthermore, all patent applications are published around 18 months after filing, so they can serve as a valuable information resource.

A patent owner can benefit from obtaining a patent for an invention. However, society also benefits. This is because, once the 20 year monopoly is up, the invention as described is freely available for others to use. This is a fundamental tenet of patent systems: patents provide an incentive to invent and innovate, and at the same time encourage disclosure of the invention so that it is "donated" to the sum of human knowledge once the monopoly expires.

The Case for Patenting Pharmaceuticals

Patent laws in almost all countries include various statutory exceptions to patentability. In other words, there will be certain subject matter for which it is not possible to obtain a patent. In the UK and Europe, these exceptions include methods of medical treatment. Although medical methods cannot be patented in the UK or Europe, in contrast, a substance or composition *for use* in a medical method is allowed. The rationale for this is that a doctor or surgeon must be free to offer the

best treatment available, in accordance with medical law, without fear of legal consequences. The infringer of a product patent protecting a pharmaceutical would generally be a manufacturer or a big pharmaceutical company, whereas the infringer of a method patent would be the doctor (or the hospital); the actual care-givers should be protected from patent infringement actions.

Of course, there are those who disagree with the possibility of patenting pharmaceuticals at all. They will argue that it is not a good thing that people can own and therefore charge a premium for life-saving medical treatments. However, the entire point of the patent system is to encourage innovation. This is particularly needed in the field of medicine and drug development. Drug development is an expensive process requiring huge investment. It can therefore be argued that the patent system encourages investment in the development of new medicines.

Developing a new pharmaceutical can be a risky business. It requires firstly the discovery of new and effective active substances. These must then be developed into formulations suitable for giving to patients, and which satisfy the regulatory authorities in terms of safety and efficacy. There is a very high failure rate.

It has been estimated that for every compound that eventually makes it to market after pre-clinical and clinical trials, 5-10,000 compounds may have been synthesised and then found wanting at some point during the approval procedure. The cost of bringing a new pharmaceutical product to market has been estimated to be somewhere between $200 million at the lower end of the scale up to $2.6 billion. This takes into account investment in products that do not make it as far as launch: more than 90% of drug candidates that reach even the clinical testing phase will ultimately fail and not make it to market.

A successful blockbuster drug can generate sales of more than a billion dollars per year, but such successes tend to be the exception, not the rule. In fact, only around 1 in 3 drugs launched is profitable. Approximately 70% of the cost of bringing the product to market occurs after initial discovery i.e., during the development stage. Companies simply would not bear these costs if they could not get some sort of protection and reward for their investment, allowing them to recoup the costs involved in development. Simply put, without incentives it is unlikely that private sector entities would undertake such R&D. Companies must be able to cover their costs (and, in most cases, have the opportunity to make a profit).

Furthermore, as noted above, patents provide a “time-limited” monopoly. Once protection expires most drugs can be copied relatively easily. By way of example, the

price of the cholesterol-lowering drug Lipitor fell by 95% in the face of generic competition after patent expiry.

A patent application must be filed before any public disclosure of the invention. This means that patent applications must be filed very early on in the life-cycle of a drug. It can take several years for a patent to be granted (often at least five years), and it can take even longer for a commercial product in the pharmaceutical sector to be launched. A patent expires 20 years from its filing date. As a result, once a pharmaceutical is launched it is not unusual for there to be only a few years of patent protection remaining, which is not very long for the patent owner to recoup the cost of bringing that drug to market. Therefore, even with patent protection, companies only have a limited time to take advantage of their monopoly to maximise profits.

Patents provide the incentive for companies to undertake the risks involved in developing drugs, and allow them the opportunity to recoup the costs involved by charging a premium whilst they have a monopoly.

What about the Developing World?

Pharmaceutical companies tend to concentrate their R&D resources on diseases prevalent in US, Europe and Japan from where they will get the vast majority of their revenues.

Problems can arise in the case of diseases that are prevalent in developing world countries, especially where people in those countries may be at risk from diseases that are not also a big problem in more economically developed countries. This is because the purchasing power of those in need is not sufficient to compensate a company for its investment in R&D for the drugs they require. The return on investment for drugs for diseases prevalent in developing countries can therefore be close to zero because patients cannot afford the high prices for those drugs. Arguably there is therefore little incentive for private pharmaceutical companies to invest in R&D into new treatments for such diseases.

Although much is known about parasites leading to diseases important in the developing world, such as the malaria parasite and trypanosomes, successful compounds may not enter costly clinical development due to this lack of financial incentive.

Currently only around 10% of health research is devoted to conditions accounting for 90% of the diseases that afflict humans around the world. How can pharmaceutical companies be encouraged to carry out R&D for treatments for diseases prevalent in the developing world? How can they recoup their investment? And how else can different entities, whether private or public, be encouraged to invest in R&D into treatments for developing world diseases?

There have been some examples of pharmaceutical companies donating products for use in the developing world. For example, back in the 1980s Merck donated ivermectin for river blindness free of charge for as long as needed to any country that requested it.

More recently, Glaxo instigated a policy to assist developing countries. It committed to R&D targeting developing world diseases and preferential pricing of drugs and vaccines for those diseases. In 2016 Glaxo also pledged not to seek patent protection in the poorest countries: all existing and future Glaxo medicines would be made freely available for generic manufacturers to produce in countries classified by the World Bank as Least Developed (or low-income) which includes more than 60% of Africa. In lower-middle income countries, Glaxo would file for patents but seek to agree licences with generic producers for a low royalty fee. Glaxo pledged only to seek the strongest protection on its products in high- and upper middle-income countries.

Whilst such gestures by drug companies are to be welcomed, supply may not meet demand.

Alternative Business Models

Several alternative business models have been suggested, which may be better suited to provide funding for R&D into treatments for developing world diseases. These models may involve a reward that is not dependent upon patents and exclusivity and high prices for the drugs, possibly enabling drugs to be more accessible to patients in the developing world.

For example, there is the Prize Model. Prizes have been used as incentives for innovation for centuries. A lump sum is given as a reward for developing a new medical tool or for overcoming a significant scientific barrier to developing a new

product. Rather than paying for R&D through high prices charged once the product is launched, prizes pay for the R&D through an upfront payment, and then introduce competition so that prices for the product can be kept low. The prizes can also ensure that R&D is directed towards areas of greatest medical need, and since the specifications for winning the prize are set at the outset, developers work to create a product according to those specifications.

Prizes can be large or small, but must be designed carefully to ensure that the reward that is offered provides a sufficient incentive to encourage developers to focus on the specific challenge set by the prize.

Another incentive that has been suggested is known as a "Priority Review Voucher". It has been estimated that if approval of a blockbuster drug is accelerated by a year, a company could increase sales by USD 300 million - a not insignificant amount. A drug company may thus be incentivised to develop therapies for neglected diseases by being awarded a voucher for priority or accelerated approval review for one of its successful, more profitable drugs.

A voucher might be awarded, for example, where a therapy treats a neglected disease, has been approved by a relevant agency such as the European Medicines Agency, has been found to be clinically superior to an existing product, and where the company foregoes patent rights and finds at least one manufacturer for the product. The voucher then entitles the bearer to priority approval review for another drug. The drug company is therefore encouraged not to seek a patent on the drug for the developing world disease, but to recoup the cost of its investment via another product, the profits on which may be increased due to the priority review.

Philanthropic organisations such as the Bill and Melinda Gates Foundation and state funding such as the EU programme for "accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction" can also have a role in encouraging development of drugs for developing world diseases without requiring a return on the investment.

There is an argument that the development of drugs against developing world diseases needs to be a charitable effort rather than a profit-making one because the free market does not incentivise the R&D required for drugs for such diseases, with or without patent protection. However, the most effective drugs against diseases prevalent in the developing world have been covered by patents. Patent owners pursue pricing strategies designed to maximise their profits, which does not

necessarily mean making the drug expensive. In fact, it simply makes no sense for a pharmaceutical company to price a drug out of reach of those in need.

WTO and TRIPS

It might be tempting to wonder why developing countries bother with patent laws at all. Why do the Governments in these countries not legislate such that competition from generic drugs can lead to lower prices for the patients in need? The answer lies with the World Trade Organization.

The WTO was set up in 1995 to ease trade negotiations between members, and currently has 164 members. WTO members are located throughout the world, and include not only developed countries, but also many countries of the developing world in South America, Africa and South East Asia.

Setting patent standards was one of most contentious issues negotiated in setting up the WTO. Through TRIPS (Trade-Related Aspects of Intellectual Property Rights), minimum standards for certain intellectual property rights are stipulated. The WTO requires all member countries to allow patent rights on pharmaceutical products and to provide a minimum term of the previously mentioned 20 years of exclusivity from the filing date of a patent application.

TRIPS also has a data exclusivity provision, which specifies that data submitted to drug regulatory authorities for obtaining marketing authorisation cannot be relied upon by a generics manufacturer (for a certain period of time). Generics manufactures must thus generate their own test data. This data exclusivity can therefore also delay the introduction of generic drugs onto the market.

Is it fair that developing countries should feel compelled to set up a patent system, which potentially allows pharmaceutical companies to sell drugs in those countries at inflated prices? TRIPS does have a provision that countries that are designated amongst the Least Developed Countries (that is, the 48 poorest nations) do not have to comply with TRIPS until 2034. Some would prefer Least Developed Countries to have indefinite extensions, or at least be exempt until they are no longer classified as Least Developed Countries. These countries could then develop their own pharmaceutical industries in the meantime so that they can have direct access to cheap medicines rather than being reliant on overseas pharmaceutical companies.

Reasons for Poor Access to Medicines

Some may argue that the patenting of medicines for use in the developing world leads to those medicines being priced out of patients' reach. However, TRIPS is not the root cause of the lack of access to medicines - there were access problems prior to this.

People in developing countries may have poor access to medicines they require for several reasons. Some developing countries have no patent laws at all and the cost of generic drugs is still too high for most people in need. There may be chronic underfunding of health infrastructure, a lack of clinics and accessible hospitals, a lack of political will, cumbersome drug regulatory procedures, high taxes and tariffs, poor distribution, low numbers of trained healthcare providers, high patient illiteracy, and/or cultural stigma to certain diseases that discourages patients from seeking help.

If patenting of drugs were not allowed, innovation could stop altogether. Citizens of poor countries would be no better off and everyone else would be much worse off.

How can these problems be reconciled? How can inventors be rewarded for their innovation, and companies compensated for their investment, whilst still enabling patients in the developing world to afford the medicines they need? How can a patent system recognise differences in different countries' well-being and at the same time encourage the private sector to become involved in creating new products for the developing world? What practical solutions are there?

Alternatives to "Big Pharma"

Public-Private Partnerships are one way of successfully bridging the gap. These combine the strengths of each party to satisfy both the public interest (that is, increased R&D) and private interests (i.e., profit).

Such partnerships should result in benefits to both parties. The public partner receives the advantage of private expertise in conducting clinical trials and obtaining marketing approval. Contractual arrangements could stipulate that distribution and sale must be at low enough prices to promote access. Exclusive licences might be allowed in developed countries whilst requiring several suppliers to increase competition in developing countries.

The benefits for the private industrial partner include positive public relations, receipt of resources to conduct the basic research, and provision of additional training and education for their own employees. Private industry may be able to obtain rights in "for-profit" markets, for example, antimalarials for travellers. Intellectual property can therefore be leveraged by being exercised in high-income markets to subsidise the cost of medicines for poorer people in developing countries.

Intellectual property can therefore be a critical tool to manage public-private partnerships and to encourage development of medicines for the treatment of neglected diseases.

Product development partnerships are another option. The Medicines for Malaria Venture is an example of a product development partnership. Many antimalarial drugs are a result of a partnership between a pharmaceutical company and the Medicines for Malaria Venture. Its mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs. Prices are set at a level affordable for public sector health services and distribution requirements are suited for all endemic countries.

The Medicines for Malaria Venture was created to fill the gap left by market failure due to lack of drug research for malaria. It provides malaria drug development expertise to its partners, it also supports joint R&D projects with funds raised from government and philanthropic sources, breaking the link between R&D expenditure and price.

The Medicines for Malaria Venture has extensive partnerships partially governed by a pragmatic approach to intellectual property. It leverages the power of intellectual property owned by its partners and ensures that the antimalarials it develops with partners reach the people who need them. It aims to take advantage of both open drug discovery and protected drug development. Protected drug development is reserved for compounds having a new mechanism of action and which appear particularly promising. Patent protection is generally not sought in malaria-endemic countries but is in developed world countries in case a lucrative second medical use for a given compound is later discovered. Intellectual property is used as a tool to attract industry partners, an incentive to conduct research, and a guard against misuse of innovation.

When the Medicines for Malaria Venture enters into contractual relationships with its partners, its primary goal is to ensure that the antimalarial drugs it develops and launches will be accessible to those most in need in malaria-endemic countries. In terms of intellectual property, the Medicines for Malaria Venture requires that the licences it takes are exclusive, worldwide, royalty-free, and transferable. This initiative therefore combines the strengths of open innovation and intellectual property protection.

The Medicines for Malaria Venture was borne out of the malaria work done by the Drugs for Neglected Diseases Initiative, which now focusses on other developing world diseases including leishmaniasis, sleeping sickness, and Chagas disease. The Drugs for Neglected Diseases Initiative aims to improve the quality of life and the health of people suffering from neglected diseases by using an alternative model to develop drugs for these diseases. This not-for-profit model is driven by the public sector. A variety of players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven R&D.

Another initiative is the Medicines Patent Pool, a United Nations-backed public health organisation working to increase access to HIV, hepatitis C and tuberculosis treatments in a group of up to 127 low- and middle-income countries by negotiating large-scale licensing agreements between drug developers and multiple generics manufacturers.

The Medicines Patent Pool aims to address one of the main challenges in fair access to treatment by ensuring there are multiple sources of affordable, quality-assured medicines for use in developing countries. The sharing of technology and patents is key to this initiative. Patent holders agree to license their medicines to the Medicines Patent Pool. The Medicines Patent Pool then licenses the rights of manufacture of these treatments to generic pharma companies. The licence terms encourage the sale of low-cost versions of the medicines. This leads to new treatments becoming available faster in developing countries, whilst the generic competition brings prices down. More people therefore gain access to the medicines they need.

Although currently only focussed on HIV, hepatitis C and tuberculosis, there is no reason why a model based on the Medicines Patent Pool should not work for other diseases mostly prevalent in the developing world.

Control of Patent Enforcement

The examples above demonstrate how careful negotiation of patent licensing terms can provide important intellectual property rights for organisations and entities outside "big pharma" to enable drug development to be carried out, and for the subsequent drugs to be available to those in need at affordable prices. However, it is worth noting that patents do not necessarily result in high prices and absolute exclusivity, putting the drugs they cover out of reach of those in need. Much can depend on how they are enforced within a country, and that can differ depending on a specific country's interpretation of patent law.

Although TRIPS sets out that drug patents lasting a minimum of 20 years from filing must be available in WTO member states, it does not stipulate other aspects of patent law, those that often arise through developing case law within a country. For example, should a patent extend to cover compounds that are "equivalent" to a patented drug (for instance, compounds that are structurally different but have the same function)? How high a bar should be set in the assessment of whether a new compound, or a new use of a known compound is "non-obvious"? These issues are within the power of the individual state/courts to decide, and this can be done so as to benefit those in need, perhaps by weakening the patent protection available.

TRIPS also provides for "compulsory licensing", which is the granting of licences to generic manufacturers to make drugs more cheaply *without* the consent of the patent holder if certain conditions are met. It is generally necessary to show that negotiations with the patent owner have previously been held. However, such conditions can be waived in national emergency or other circumstances of extreme urgency. States can choose how compulsory licences may be used so these could be related to public interest, or public health for example. TRIPS therefore allows governments some rights to override patents in emergencies.

An approach of differential patent protection has been suggested, in which patent protection across lower-income countries differs across diseases depending on the importance of those countries' markets as a potential source of research incentives. Protection could strengthen as a country becomes richer and its market significant. People in developing countries suffer as much, if not more so, from diseases such as heart disease and cancer that are prevalent in more developed countries. Patents on drugs for those diseases in developing countries contribute only a very small proportion of the profit for the pharmaceutical companies. The incentive for R&D for diseases common also in developed countries comes from profits made in developed countries.

Extending patent protection in developing countries to incentivise research on diseases such as malaria makes sense; strong patent protection in developing countries for diseases such as cancer less so. Drug companies could be compelled to choose only rich countries to obtain patent protection for global diseases, with patents for developing world diseases being obtained only in the developing countries with relatively higher GDP. Essentially, countries with very low GDP would have no patent protection for pharmaceuticals, even for diseases prevalent there. A company's profits would be mostly generated in other developing countries in which those diseases are a problem, those countries having a relatively higher GDP.

A patent owner could stipulate in its licenses how its intellectual property may be enforced, thereby providing some downstream control of the technology. Universities that obtain patents could compel licensees not to enforce those patents in developing countries (and any follow-on patents that may be obtained by the licensee in its own right). This essentially "donates" the technology in those countries.

Conclusions

It is not patents *per se* that block access to medicines for people in developing countries, rather how they are used. The patent system is not perfect, but it can be tweaked if the will is there. This needs to go hand-in-hand with other changes, such as increased partnership between governments of developed and developing nations, increased funding and retention of healthcare workers, and improvements in health infrastructure.

Although the system we have is not perfect, it is the best workable system that society has managed to develop, and which has been used to reward inventors for innovation for centuries. It has of course evolved during that time, and will continue to evolve, hopefully for the benefit of society at large.

Further Reading

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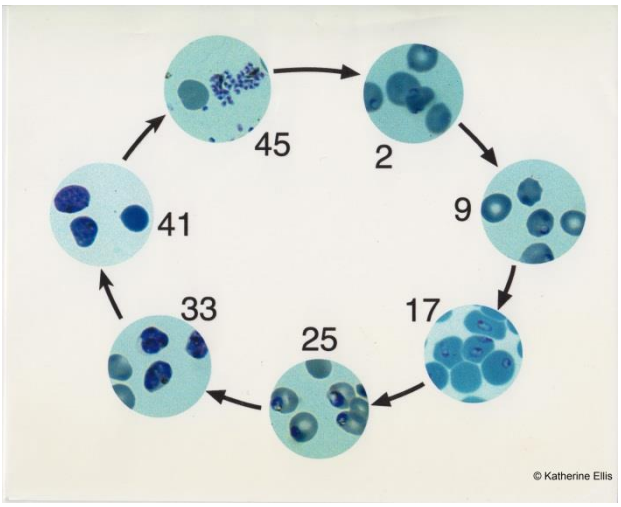

The erythrocytic cycle of *Plasmodium falciparum* (hours)