Beyond Patents: Scientific Knowledge, and Access to Vaccine

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Summary

Knowledge is a public good. Patents provide property rights in knowledge, which gives the patentee the right to exclude others from utilising the knowledge for the life of the patent. Patents in the field of pharmaceuticals are controversial because of the importance of the knowledge which they exclude others from using. Patents have come under significant criticism for this very reason – with some going as far as to claim that patent protection on pharmaceutical products as the cause of developing states having poor or limited access to life-saving pharmaceutical products. The majority of the academic literature regarding access to medicines presents patent protection on pharmaceutical products as the cause of developing states having poor or limited access to life-saving pharmaceutical products. This paper challenges this viewpoint, and considers the barriers to generic access to medicines beyond patents. This paper looks beyond intellectual property rights to determine what other mechanisms exist that allow innovative vaccine manufacturers to control access to knowledge regarding their products which can act as a barrier to the utilisation of knowledge in the pharmaceutical industry, in a similar manner to intellectual property rights. This paper takes a case study approach considering non-patent related barriers to access to medicines, focusing on pandemic influenza vaccines and the role of proprietary, non-patented knowledge. This paper concludes that manufacturers have an exclusive monopoly, not because of their intellectual property rights, but because the knowledge required to make the drug is not accessible to generic manufacturers, and highlights why this is the case. This paper argues that it is not the patent protection which is the barrier to introducing generic pandemic influenza vaccines, but rather it is the inaccessibility of knowledge which is not in the public domain, or the inability of manufacturers in developing states to utilise this knowledge, which is the true barrier in this field.

Résumé

La connaissance est un article collectif. Les brevets fournissent les droits de propriété sur cette connaissance, donc le breveté peut exclure les autres d'utiliser la connaissance pendant la durée du brevet. Les brevets pour les médicaments sont sujet à controverse à cause de l'importance du connaissance qu'ils les exclurent d'utiliser. Les brevets ont tombé sous la critique pour cette raison - avec certains qui déclarent que les inventions médicaments brevetées sont cause des états en voie de développement ayant l'aces faible ou limité au médicaments de sauvetage. La majorité de la documentation académique au sujet d'accès à médicaments présentent les inventions médicaments brevetée d'être la raison pour des états en voie de développement ayant l'aces faible ou limité au médicaments de sauvetage. Cette article conteste ce point de vue, et il considère les barrières à l'accès générique du médecins autre que des brevets. Cette article examine au delà des brevets afin de déterminer les autres mécanismes qui permettent des fabricants des vaccines innovateurs limiter l'accès a la connaissance sur leurs produits. L'article examine si ces autres contrôles peut avoir des résultats similaires au brevets, et protège le droits des fabricants sur la connaissance de leurs produits. Cette article se fonde sur une étude de cas au sujet des obstacles autant que des brevets, et il se concentre sur des vaccins contre la grippe et la rôle de la connaissance propriétaire qui n'est pas au sujet à brevet. Cette article conclut des fabricants ont un monopole, pas parce qu'ils ont des brevets, mais parce que les fabricants génériques ne possèdent pas la connaissance qu'il faut avoir pour la production des médecins, et cette article explique pourquoi c'est le cas. Cette article soutient que ce n'est pas le brevet qui empêche l'introduction des vaccins génériques, plutôt, c'est la connaissance inaccessible qui n'est pas dans la domaine publique, ou encore l'incapacité des fabricants dans les états en voie de développement d'utiliser la connaissance qui constitue le vrai contrôle en cette situation.

Introduction

Patents provide property rights in knowledge generated by way of an invention. In pure economic terms, knowledge is a public good; an intangible asset of which anyone can consume as much of as desired, without diminishing the amount available for others [1-3]. For example, the knowledge required to manufacture aspirin could be transferred from Person A, to Persons B, C, D and E, without diminishing Person A's knowledge. Once a public good is created it is difficult, or impossible, for the creator to stop people from using it who have not paid for it; [1] this is commonly known as the free rider problem [4]. The free rider problem is considered undesirable within economic markets as businesses cannot charge for each unit of a public good that is consumed, meaning that there is little incentive to generate, produce or enhance public goods [5]. If a public good is just as useful to society as a comparable private good, then it can typically be said that the public good is under-produced and that this is inefficient for the society as a whole [6].

Patents move knowledge from being a public good, where there is no legal control over dissemination, to being an intangible asset which a person or organisation may have property rights in. A patent grants the patentee the right to exclude others from utilising the knowledge, for the life of the patent [7]. Patents in the field of pharmaceuticals are controversial because of the importance of the knowledge which they exclude others from utilising. The academic literature concerning patents and pharmaceuticals can be rather crudely divided into two camps: those who argue that awarding patent rights over pharmaceutical products, even if they are life-saving, is justifiable, as without such patent rights pharmaceutical companies will lack the incentive necessary to invest time and money in drug creation in the first place; [8-10] and those who argue that awarding patent rights over pharmaceutical products is unjustifiable, on the basis that awarding patents on pharmaceutical products diminishes access to these products, with undesirable repercussions for healthcare, particularly in developing states. This argument is based on the fact that a patent will provide a pharmaceutical manufacturer a monopoly over a potentially life-saving product, and the patent affords the manufacturer the power to control production and distribution, and artificially

inflate its price, should they choose to [11-15]. It should be noted that arguments to justify the patent system sit along a spectrum, and the dichotomy highlighted above represents some of the more polarised opinions in the literature.

This debate has focused on the exclusionary rights granted to patent holders, which prevent third parties from making, using, offering for sale, selling or importing for these purposes that product, without the express consent of the patent holder. This limits generic competition, which is the biggest contributor to price reduction in pharmaceutical products [16]. With price reductions inevitably comes increased access, particularly in developing states [17]. The debate regarding the extent to which these exclusionary rights can negatively impact upon the right-to-health largely stems from concerns over access to HIV/AIDS medicines in developing states [18-20], though it has subsequently been translated to other public health concerns, particularly in developing states [19].

As Cullet said, on the requirement of developing states to provide patents in the field of pharmaceuticals:

> In most developing countries, the introduction of process and product patents on drugs is likely to influence access to drugs to a significant extent. There will be abrupt rises in price, impacts on local pharmaceutical industries and a greater emphasis on private sector research and development. Together, these are likely to create a situation where drugs become both less accessible and less affordable. There is therefore a direct link between patentability of drugs on one hand and, on the other, the availability of medicines, the realization [sic] of the right-to-health and ultimately of the right to life [19].

The negative impact that the exclusionary rights granted to a patent holder can have on access to medicine, and therefore on realising the right-to-health in developing states, is well established [21]

Moreover, much literature has been generated by the academic community, and by civil society, on how to limit or eliminate this negative impact in developing states [22-24]. However, it appears that the literature concerning the impact of patents on the right-to-health in the context of access to medicines considers only oral solid drugs – tablets, not vaccines – but does so under the umbrella term 'medicines'. A considerable amount of the academic literature on access to health goods has grouped together ideas of access to solid dose drugs, and access to vaccine under the umbrella term 'medicine'. This is succinctly demonstrated by Marks and Benedict, who wrote

> [w]hile the literature has historically focused primarily on access to medicines, many of the considerations for access to vaccines and medical technologies are similar…this chapter will therefore assume a degree of commonality among these categories in extrapolating lessons from access to medicines to the broader category of health goods [25].

Such an assumption is misplaced and unhelpful. While there may be some overlap between these categories in the sphere of access to health goods, the reasons for a lack of access, and the solutions regarding how to improve access to each of these health goods, are actually quite distinct. To assume commonality of characteristics in this way automatically leads us to assume commonality of solutions, as this research goes on to argue, this commonality does not apply to pandemic influenza vaccines.

The distinction between drugs and vaccines

A solid dose drug is a product that has been 'manufactured through chemical synthesis, meaning that it is made by combining specific chemical ingredients in an ordered process' [26]. These products are rather simple chemical combinations, and as such they can be easily copied by reverse engineering by generic drug manufacturers. Reverse engineering is essentially a way of working out the 'recipe' for a drug. It involves breaking the original product down into its basic chemical components, and with the assistance of the patent application and market authorisation information,

allowing a generic drugs manufacturer to accurately identify and quantify all of the ingredients in the drug formulation, allowing them to create a bioequivalent, generic product. The only thing that prevents this from happening on a widespread scale around the world is the exclusive rights of the drug creator, typically in the form of a patent [27].

As generic bioequivalent drugs are in essence direct copies of the original product, in most jurisdictions there is an abbreviated regulatory process for bringing the drug to market [28]. This is because the generic drug manufacturer can provide the results of clinical trials that were used to originally approve the patented pharmaceutical product, in order to prove the safety and efficacy of the bioequivalent generic product [29]. This is particularly beneficial from a public health perspective as it means that during a public health emergency when a generic producer has been licensed to produce a patented product (either by the patent holder, or the national Government), the drug can be licensed, brought to market and distributed in a much shorter time frame than if it were a patented product being licensed for the first time. The benefits of generic drug manufacturers reverse engineering drugs to introduce generic versions are two-fold. First, when procuring drugs, the ability to introduce generic drugs can have a substantial impact on a developing state's abilities to procure sufficient levels of a drug, as generics are traditionally priced significantly lower than their brand-named counterparts [30]. Second, merely the threat of allowing a generic manufacturer to enter the market could been regarded as an effective public health tool, as this has been successfully used to encourage a number of patent holders to reduce the price of their patented product [31].

However, rather than being classed as a drug, a vaccine is technically a biologic, meaning that it is manufactured in a living system, typically a microorganism, or animal cells [26]. Due to the complex structure and manufacturing processes associated with biologics, it is impossible for generic manufacturers to prove that their version a bioequivalent of the original biologic [26]. This

means that any vaccine which purports to be a bioequivalent of a currently licensed product must go through the same clinical trial and licensing procedures as the original product, and is not able to use the safety and efficacy data generated by the innovator of the original product in the way generic manufacturers of oral solid oral drugs can [32].

To this end, the patentable elements of oral solid dose drugs are based on the product's composition of matter, and its application within medicine. A novel compound with pharmaceutical properties is eligible for patent protection. Pharmaceutical patenting is limited because 'a method of treatment of the human or animal body by surgery or therapy, or a method of diagnosis practiced on the human or animal body' is not eligible for patent protection. However, a patent may be granted for a first medical indication when an inventor discovers that a compound, already part of the state of the art, has a pharmaceutical application that can be used to treat a specific medical indication. Second, medical indication patents can be granted for further, specific uses of known substances or compositions. Both first medical indication and second medical indication applications must be supported by sufficient evidence to prove likely efficacy. This differs significantly from the patentability of pandemic influenza vaccines, whereby it is not just the compounds that comprise the vaccine that are patentable, but also the processes by which the vaccine is manufactured, the adjuvant, and in some instances, the inactive virus or genetic structures within the virus against which the vaccine protects. In order to determine any impact these patents have on access to pandemic influenza vaccines and the therefore the extent to which a state can discharge its right-to-health obligations during a pandemic, it is first necessary to describe the patent landscape of these same vaccines, components and processes.

Patent Landscape

Three major reports regarding the pandemic influenza vaccine patent landscape can be identified. First, in 2006 a freedom to operate exercise was carried out by Krattinger and others in the field of pandemic influenza vaccines, in order to determine what, if any, intellectual property related barriers could prevent a manufacturer from achieving freedom to operate in the field [33]. No patents regarding viral strains or components were included in this search. Second, a patent landscape report regarding pandemic influenza viruses 2005-H5N1 and 2009-H1N1 was published by the World Intellectual Property Organisation (WIPO) in 2011 [34]. This report specifically considered patents claiming inventions comprising the virus, a component, or a derivative of the virus, for diagnostic, therapeutic or prophylactic purposes, where the patent was applied for after the date at which it became clear that that strain of virus could be of pandemic potential. This report did not consider any manufacturing patents. Third, is the report by the Franklin Pierce Center for Intellectual Property, which in 2013 published the *Patent Landscape of Influenza: A Prophylactic Vaccines and Related Technologies* report (henceforward "the Franklin Pierce report") (35). This report considered both the vaccine manufacturing patent landscape, and the viral strain patents, and is therefore the most relevant to this research.

The Franklin Pierce report reached a number of interesting conclusions about the patent landscape for pandemic influenza vaccines. Firstly

> the number of patent documents related to influenza being published has been steadily increasing in the last decade…. Until the mid-1990s, there were only a few influenza patent documents being published each year. The number of publications increased noticeably when TRIPS took effect, resulting in publication of patent applications. However, since 2006 the number of vaccine publications has exploded. In each of 2011 and 2012, about 100 references disclosing influenza vaccine technologies were published [35].

Despite this ‘explosion’ the number of patent families in the field remains relatively small - and approximately 150 relevant patents can be identified that specific address pandemic influenza A vaccines, and associated technology [35]. Though it is worth noting that some more general patents may be applicable to some forms of vaccine manufacturing, though this is difficult to determine. When seeking freedom to operate in a field of technology, the number of patents is of course relevant, but so is the number of patent holders. The predominant barrier to freedom to operate that an anticommons creates is that there are numerous patent holders with whom a new manufacturer seeking to enter the market must successfully negotiate. While the Franklin Pierce report notes that ‘influenza vaccine technologies are disclosed in a fairly small set of patent documents’[35], it is also worth noting that these patents are held by a number of patentees, as the table below demonstrates.

The patents identified in the field of pandemic influenza vaccines can be divided into two subcategories worthy of further consideration. Those patents which relate to, or make use of, pandemic influenza viruses, and those patents related to the pandemic influenza vaccine manufacturing process. Each of these subcategories of patents may have an impact on the extent to which developing states are able to obtain sufficient access to pandemic influenza vaccines in order to discharge their right-to-health obligations.

Patents related to pandemic influenza viruses

Section Five of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) requires members to grant patents in any field of technology, providing the grounds for patentability have been satisfied [36], and TRIPS exemptions to patentability [37] have not been breached. TRIPS does not explicitly exclude any area of innovation from patentability – but does allow states to exclude inventions that offend *ordre public* or morality, including where it is necessary to protect human health [36], and diagnostic, therapeutic or surgical methods [36].

Despite this flexibility, many states have chosen not to exclude viruses, or VLPs, from patentability [38-40], which has met a great deal of controversy [41-45].

A number of patents identified by the Franklin Pierce Report directly make use of, and refer to, a substrain of a pandemic influenza virus, including viruses which do not currently exist naturally but may begin circulating in the future. Such patents could limit freedom to operate [46], should the genetic material claimed then be required in order to manufacture a Pandemic influenza vaccine for a circulating strain. The majority of patents relating to virus genetic material cover specific uses of the virus in a novel vaccine composition; therefore, such patents do not affect freedom to operate and 'could not legitimately be used to constrain parallel development of alternative uses of the same genetic inputs' [47], provided the virus could be used in another novel vaccine composition, not covered by the original patent, or any other patent that claims use of the genetic material in this way.

Some patents granted have applicability to a number of influenza outbreaks, both seasonal and future pandemics. For example, WO/2010/148386 [48], a patent that at first glance appears to cover a method of production for 2009-H1N1 vaccine, is not limited to the methods of production for 2009-H1N1 vaccines. It also encompasses the method of extracting and using VLPs in future pandemics. WO/2009/092038 [49], a patent claiming use of multiple H5-subtypes in a DNA vaccine, is applicable to any substrain of the H5 virus being used in a DNA vaccine manufacturing process, meaning it may have applicability beyond the pandemic for which it was developed.

If such patents remain enforceable at the time the virus begins to circulate naturally, they may hinder future research, development and manufacture of a vaccine. The existence of numerous patents, held by numerous patent holders, covering multiple substrains of the influenza virus may disincentivise future innovation in this field, because they cause an anticommons [50] and deny

sufficient freedom to operate for manufacturers. At least twenty-one different entities hold multiple, relevant patents in this field – ranging from the large pandemic influenza vaccine manufacturers to national governments and small biotech research labs. While it is true that in order to obtain freedom to operate, a new manufacturer would not have to negotiate for a license with all these patent holders, only the patentee of the technology one wishes to make us of, this is still a difficult, time-consuming task. It may be so difficult as to be a disincentive to those manufacturers considering entering the market [50]. In addition, while the research exemption [51] contained within many states' domestic patent laws may enable some degree of research on the patented virus or virus particles, should this research lead to a viable vaccine, the patent may prevent it reaching the market if a license cannot be negotiated on terms reasonable to both parties [52].

Patents related to manufacturing process

There is a growing trend for patents on vaccine manufacturing processes, as was noted at a WHO seminar on patents and vaccines: 'older patents were used to protect components of vaccines (organisms, antigens and conjugates), while recent patents tend to protect methods (expression system, platform technologies, purification process, formulation or even delivery devices)' [53]. This shift has coincided with advances in the extraction, purification and production methods for pandemic influenza vaccines.

Patents on reverse genetic engineering technologies, which are a key new technology for the production of egg-based pandemic influenza vaccines, have been identified as a barrier to production for competitors [54]. Moreover, pandemic influenza vaccine manufacturers appear to be moving towards utilising new methods of growing viruses for vaccine production, each of which has some degree of IPR that has been identified as a potential barrier to access for competitors: firstly, cell-based influenza vaccines, the manufacturing of which is subject to 'many intellectual property impediments. These include patents on cell lines and production systems, as well as trade

secrets on safety profile of cells' [55]; live attenuated vaccines, where 'intellectual property impediments exist on the use of strains; and patents and trade secrets cover the formulation. Seeds may need reverse genetics' [55]; and finally 'second generation biotech' such as DNA vaccines where 'impediments will depend on specific technology…it may be anticipated that these technologies will have robust IPR coverage as they are mainly being developed by biotech companies and universities seeking to sell this technology' [55].

Both the patents on pandemic influenza viruses, and those on the manufacturing processes outlined above, could reduce access to pandemic influenza vaccine in developing states by limiting the number of manufacturers in the market space or preventing new manufacturers from entering the market, because these manufacturers do not think they can achieve freedom to operate. From an access, and right-to-health perspective, this is concerning for two reasons. First, as a major study regarding the prices, availability, and affordability of medicines in thirty-six developing and middle-income countries found, the greater the number of manufacturers of a pharmaceutical product in a market, the cheaper the cost of that product [16]. With cheaper cost for the product clearly comes better access, particularly for developing states. Second, an increase in the number of manufacturers in the market place for pandemic influenza vaccines should lead to an increase in overall vaccine manufacturing capacity. This would increase the self-procurement options that were available to a developing state. With greater procurement options, a developing state may be able to contract with a manufacturer that did not have to satisfy an advance purchase agreement contract during a pandemic, meaning the developing state could access the vaccine more quickly.

The Effect of Patents on Procurement of Pandemic Influenza Vaccines

Patents and Prohibitive Prices

A pandemic influenza vaccine costs the state approximately £3.50 per dose (excluding administration) [56], and in order to establish full immunity against a pandemic strain a two dose strategy is typically required [57]. Therefore, the cost of an influenza pandemic vaccination programme is likely to be very high, and in some instances may be prohibitive, particularly to developing states. This point is demonstrated by the fact that ninety-five states were deemed to have a 'lack of ability to purchase vaccine on the commercial market' during 2009-H1N1 [58], and a review of the WHO Vaccine Deployment Initiative later noted that 'the cost of deploying vaccine was a constraining factor that limited the quantity of pandemic H1N1 vaccine demanded by countries' [59].

It is clear that one of the reasons these ninety-five developing states were unable to meet their right-to-health obligations to ensure provision of…immunization programmes against the major infectious diseases was the cost of the vaccine. As to the role patents play in prohibitive prices of pandemic influenza vaccines, some commentators have claimed that the existence of patents are the cause of high drug prices [60, 61]. From a right-to-health perspective, as noted above, in using their exclusionary rights to prevent generic competition in the market for a life-saving drug, patent holders may negatively impact upon an individual's right-to-health, where that individual is prevented from accessing the life-saving drug due to the lack of cheaper generic versions. However, this linking of the existence of patents on a pharmaceutical product to the high price of a pharmaceutical product could be seen as too simplistic a standpoint.

It may be the case that the patents this paper have highlighted, and high prices are inextricably linked. Generic drugs are traditionally priced significantly lower than their patented counterparts [16], and the more generic providers that exist, the greater the reduction in price [54]. The reasons for this are straightforward: generic manufacturers incur significantly lower costs than the innovator, as they bear none of the costs of research and development, nor the licensing of the drug.

Therefore they can afford to offer the product at a reduced cost, while still being profitable. This either leads to the generic product being purchased, or the competition from the generic provider forcing the innovator to reduce their prices, in order to maintain sales.

However, it is not the existence of the patent that is the cause of high price *per se*, as patent protection does not necessarily mean that the price of a product will be high. A patent however, does ensure the patentee can maintain their monopoly, and the monopoly in turn provides the climate for the patentee to charge the price they wish, without the fear of imitators undercutting them. It is the manufacturer having the ability to exploit a monopoly that causes the high prices of medicines, not merely the existence of the patent. The price of pandemic influenza vaccines would not necessarily be lower if the patentee's exclusive rights could be circumvented. 'Natural' monopolies are also caused by other factors, such as a manufacturer's dominant market position, or it being financially or practically prohibitive for generic manufacturers to manufacture or license a product. The ongoing public debate about the price rises for *Daraprim* in the United States of America is testament to that fact [62, 63]. Turing Pharmaceuticals manufactures and sells *Daraprim* in the United States of America. *Daraprim* is an antiparasitic, commonly used to treat HIV patients that became headline news when the price was increased from $13.50 to $750 per pill in late 2015 [64]. Turing Pharmaceuticals was able to increase the price so substantially because it holds a monopoly over the sales and distribution of *Daraprim*. However, this monopoly is not provided by a patent; the patent for *Daraprim* expired over sixty years ago.(65) Turing Pharmaceuticals' exclusive rights to sell *Daraprim* comes from the company holding the only marketing license for *Daraprim* in the United States of America [66]. In this case a monopoly is preventing cheap generic access, but it is not because of intellectual property, as some of the literature would lead one to think.

In general, patent protection may inhibit the procurement of cheap medicines by blocking the entry of generic rivals, whose presence increases availability of the product, and is likely to lead to a price reduction. Generic entry benefits the drug procurement processes of developing states by offering them an alternative, cheaper manufacturer to buy from, or by encouraging the innovator to reduce their price in order to respond to the competition in the marketplace. However, since there are no generic manufacturers for pandemic influenza vaccine, it is does not appear that it is solely the patent that maintains a monopoly for pandemic influenza vaccine manufacturers. On the contrary, it appears that pandemic influenza vaccine manufacturers have a strong monopoly, and are at little to no risk from generic competition, regardless of the patents granted on the vaccines they produce.

Blocking competitors and pandemic influenza vaccine procurement

When discussing a patentee's exclusive rights, one may be forgiven for thinking that these rights merely stop imitators from making 'carbon-copy' replicas of the patentee's invention, and selling it for a significantly reduced price. This argument does not consider that a patent may also serve to block rival innovations. To this end, it is necessary to mention patent thickets [67] and the tragedy of the anticommons metaphor. A patentee that holds patents related to pandemic influenza viruses may choose not to license the use of the patented virus, or virus like particles, to a rival innovator firm, just because they are rivals in such a small market. The main purpose of the patents in pandemic influenza vaccine technology may be to block innovation by rival firms, by creating an anticommons, rather than blocking generic manufacturers. As a result, it may be difficult for rival innovators to bring a novel pandemic influenza vaccine to market without potentially infringing another innovators patent. This inhibits the number of vaccines available for procurement by states, by creating a scenario in which growth in vaccine manufacturing capacity is reliant upon current manufacturers choosing to expand their production capacity, which there is presently no market incentive to do [68-71].

In order for an innovator to overcome this patent barrier, they would need to negotiate a license with the patent owner, or create a new product or process that does not infringe on any patents. As Kane noted, a manufacturer's position is significantly strengthened in such negotiations if they hold a relevant patent that may be being infringed:

> Patented compounds or methods required for vaccine production must be purchased or licensed from commercial entities who may hold patents on any of these items. The willingness to license or the licensing terms may reflect the patent-related considerations that enter the transactional evaluation. A patent could affect licensing negotiations through pricing mechanisms or limited offerings [72].

This means that capacity, and thereby procurement, will not be improved by new innovators, because the incentive to enter the market is not sufficiently strong, or they are unable to bring their innovation to market because of an inability to reasonably negotiate licenses with numerous patent holders.

Such a situation has not yet occurred in pandemic influenza vaccine reverse genetics manufacturing [73], and freedom to operate is possible in this field. Prior to late 2005, at least four institutions had to approve licenses in order for a pandemic influenza vaccine manufacturer to obtain freedom to operate in the reverse genetics vaccine field [74]. Reverse genetics is a key technology in stabilising pandemic influenza viruses for their inclusion in vaccines. In late 2005 MedImmune secured exclusive licensing rights to all key patents from the different rights holders [75, 76], and the company has given assurances that that research and manufacturing licenses would be issued to relevant parties [76], ensuring freedom to operate exists in the field.

However, the situation is far from ideal; freedom to operate in influenza vaccine reserve genetics is only possible at present because MedImmune 'has taken steps to ensure that its patent rights do not inhibit the development and commercialization of a pandemic influenza vaccine' [76] and has

notified the WHO that that it would grant free access to its intellectual property to government organisations and companies developing pandemic influenza vaccines *gratis* for public health purposes [76]. Yet the commitment MedImmune has given is not legally binding, meaning such licenses could be withdrawn or refused by the company, and there is no guarantee that they will be as forthcoming with licensing of technology in the future. Finally, reverse genetic engineering is merely one of a number of potential avenues for pandemic influenza vaccine development, and no such guarantees have been given by the patent owners in the other areas of influenza vaccine research and development, meaning that freedom to operate may not be as easily achieved in DNA vaccines or cell-based influenza vaccine manufacturing.

Locking up knowledge - beyond patents

Peter Drahos claims that, if profit is to be made from abstract objects which are 'non–rivalrous' [77] in their consumption, then in order to maintain a system of incentivisation the rights to these public good 'have to be locked up in some way, at least temporarily' [78, 79]. In theory, the claims made by Drahos and Nordhaus that patents adversely affect the efficient use of knowledge by restricting, or 'locking up' knowledge have some merit, after all the fundamental purpose of a patent is to control the use of the knowledge generated for the life of the patent [78]. While it is entirely correct that patents are an effective way in order for innovators to 'lock up' knowledge, it is important to acknowledge that a patent is not the only way in which the dissemination and use of knowledge can be 'locked up' by an innovator. In the case of pandemic influenza vaccines, knowledge is locked up by key information required in order to manufacture pandemic influenza vaccines not being placed in the public domain, and not being made available outside of the small number of established pandemic influenza vaccine manufacturers:

> the technical know-how − even of conventional egg-derived influenza vaccines − is not readily found outside existing influenza vaccine production plants. Thus, even for

> procedures for which there are no patents, securing working partnerships with technology holders may be necessary [80].

Access to, and an ability to make use of proprietary, non-patented knowledge, that is not available outside of the established pandemic influenza manufacturers is clearly a barrier to new manufacturers entering the pandemic influenza vaccine market, be they generic or innovative. In addition to this, an inability to make use of this of proprietary, non-patented knowledge also limits the extent to which developing states can make use of use without authorisations of the right holder provisions, in order to introduce generic drugs within their territory. This is particularly concerning from a right-to-health perspective, as it is these provisions which developing states typically make use of in order to increase access to patented medicines. To this end, the quotation from Pasteur that "Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world" [81] is certainly admirable in its sentiment. However, it is not reflective of how the knowledge generated in modern science is managed and distributed, particularly in the field of pharmaceutical research and development. In light of this quote, a person interested in access to pharmaceutical products may be compelled to direct their mind to the question 'How do we arrive at a scenario whereby knowledge of how to manufacture pharmaceutical products does belong to humanity?' This question would likely lead them to the answer of abolishing a system that allows for the knowledge of how to manufacture pharmaceutical products to be owned by individuals: the intellectual property system.

However, during this paper the argument has been advanced that knowledge not locked up by the intellectual property system is actually the significant barrier to new manufacturers entering the pandemic influenza vaccine market, particularly in developing states. Those of us interested in access to pharmaceutical products appear to be directing our minds to the wrong question. The question ought not to be 'How do we arrive at a scenario whereby knowledge belongs to

humanity?' but rather 'How to we ensure that knowledge, regardless of who it belongs to, is usable by humanity?' It is this distinction between ownership of knowledge, and ability to use knowledge, regardless of ownership, that I argue is the crux of this matter. It is noteworthy that the key information that manufacturers in developing states would need access to in order to establish manufacturing capacity is not 'owned' in any formal sense, in that, no property rights have been granted over this knowledge by way of intellectual property. A lack of property rights over this knowledge would typically lead us to the assumption that this knowledge is therefore utilisable by humanity, because there are no property rights preventing utilisation occurring, however, as this thesis has demonstrated, this is not the case.

Conclusion

There are multiple elements of a pandemic influenza vaccine, and its manufacturing processes that can be, and are, patented. To some degree, such patents have the potential to hinder procurement of pandemic influenza vaccine by creating barriers to entry for new manufacturers - barriers that look set to be reinforced with the move to utilising patented manufacturing technology, such as cell-based and live attenuated influenza vaccine technology. Such barriers affect access to pandemic influenza vaccines by limiting the number of manufacturers that can utilise this technology and enter the market. This in turn limits the overall manufacturing capacity for pandemic influenza vaccines, and limits the self-procurement options for developing states; both of which reduce the ease with which developing states can discharge their right-to-health obligations during an influenza pandemic.

References

[1] Samuelson PA. The Pure Theory of Public Expenditure. The Review of Economics and Statistics. 1954;36(4).

[2] Samuelson PA. Diagrammatic Exposition of a Theory of Public Expenditure. The Review of Economics and Statistics. 1955;37(4).

[3] Samadi S. The New Palgrave Dictionary of Economics. IV ed. Eatwell J, Miligate M, Newman P, editors. New York: Palgrave Macmillan; 1987 Nov 26.

[4] Scotchmer S. Innovation and incentives. Cambridge, MA: The MIT Press; 2006 Sep 1.

[5] Touffut J-P. Advancing Public Goods (The Cournot Centre for Economic Studies Series) Edward Elgar Publishing; 2006 Aug 6.

[6] Oakland WH. Public Goods, Perfect Competition, and Underproduction. Journal of Political Economy. 1974;82(5).

[7] Although there are some limited circumstances in which a patented product can be exploited without the consent of the patentee.

[8] Grabowski H. Patents, Innovation and Access to New Pharmaceuticals. Journal of International Economic Law. 2002;5(4):849–60.

[9] Barton JH, Emanuel EJ. The Patents-Based Pharmaceutical Development Process. JAMA. 2005;294(16).

[10] For more information on how this argument related to the development of pandemic influenza vaccines see: Eccleston-Turner M. The economic theory of patent protection and pandemic influenza vaccines. American Journal of Law & Medicine. 2016 May;42(2-3):572–97.

[11] Ferrell O, Fraedrick J. Business Ethics. 1st ed. United States: Houghton Mifflin College Div; 1991 Aug 5.

[12] Spinello RA. Ethics, pricing and the pharmaceutical industry. Journal of Business Ethics. 1992;11(8):617–26.

[13] Angell M. The Pharmaceutical Industry - To Whom is It Accountable? New England Journal of Medicine. 2000;343(19):1415–7.

[14] Correa CM. Intellectual property rights, the WTO, and developing countries: the TRIPS agreement and policy options. New York: Third World Network; 2000.

[15] Sterckx S. Can drug patents be morally justified? Science and Engineering Ethics. 2005;11(1):81–92.

[16] Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. The Lancet. 2009;373(9659):240–9.
[17] Drahos P, Mayne R, editors. Global intellectual property rights: Knowledge, access and development. United Kingdom: Palgrave Macmillan; 2002 Oct 31.
[18] Cullet P. Patents and medicines: the relationship between TRIPS and the human right to health. International Affairs. 2003;79(1):139–60.
[19] Cullet P. Human rights and intellectual property protection in the TRIPS era. Human Rights Quarterly. 2007;29(2):403–30.
[20] Beyrer C, Villar JC, Suwanvanichkij V, Singh S, Baral SD, Mills EJ. Neglected diseases, civil conflicts, and the right to health. The Lancet. 2007 Aug;370(9587):619–27.
[21] 't Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access to medicines for all. J Int AIDS Soc. 2011 Mar 27;14(15).
[22] Correa C. Bilateralism in intellectual property: Defeating the WTO system for access to medicines. Case Western Reserve Journal of International Law. 2015;36(1).
[23] Shapiro C. Innovation Policy and the Economy. Jaffe A, Lerner J, Stern S, editors. Boston: MIT Press; 2011. Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting'.
[24] Pogge T, Rimmer M, Rubenstein K, editors. Incentives for Global Public Health: Patent Law and Access to Essential Medicines. 1st ed. Cambridge, UK: Cambridge University Press; 2010.
[25] Marks S, Benedict A. Advancing the human right to health. Zuniga JM, Marks SP, Gostin LO, editors. Oxford, United Kingdom: Oxford University Press; 2013 Jul 4. Access to Medical Products, Vaccines and Medical Technologies.
[26] Biotechnology Industry Organization. bio.org.: BIO. How do drugs and Biologics differ? 2014 Feb 13. Available at: http://www.bio.org/articles/how-do-drugs-and-biologics-differ.
[27] Koradia VS, Chawla G, Bansal AK. Comprehensive characterisation of the innovator product: Targeting bioequivalent generics. Journal of Generic Medicines. 2005 Jul 1;2(4):335–46.
[28] Lopert R, Gleeson D. The high price of 'Free' trade: U.S. Trade agreements and access to medicines. The Journal of Law, Medicine & Ethics. 2013 Mar;41(1):199–223. For information on the growing trend for 'Data Exclusivity' provisions in FTAs, which prevent generic manufacturers relying on the test data generated by the innovator, even when a compulsory license has been issued. This has the effect of essentially providing the innovator with a monopoly over the drug, beyond that which is provided by the patent.
[29] Raw A. Regulatory considerations of pharmaceutical solid polymorphism in abbreviated new drug applications (ANDAs). Advanced Drug Delivery Reviews. 2004 Feb 23;56(3):397–414.

[30] United States Food and Drug Administration Center for Drug Evaluation and Research. United States of America Food and Drug Administration, 'Approved Drug Products with Therapeutic Equivalence Evaluations (33rd ed.). Washington, D.C.: FDA; 2003.

[31] United Nations. Delivering on the global partnership for achieving the millennium development goals millennium development goal 8 http: // www.un.org /esa /policy / mdggap MDG gap task force report 2008. Geneva: UN; 2008.

[32] The boundaries between the exclusion of methods of treatment from patents and the patentability first medical indication has presented a considerable challenge to UK and international courts see: *Bristol-Myers Squibb v Baker Norton Pharmaceuticals* [2001] RPC 1; T 09/81 *AS-TA/Cytostatic combination* OJEPO [1983]; T 24/91 *THOMPSON/Cornea* OJEPO [1995]

[33] Krattinger A. Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics: Case Studies on Pandemic Influenza, Malaria and SARS. Innovation Strategy Today. 2006;2.

[34] WIPO. patent report on pandemic influenza preparedness (PIP)-related patents and patent applications. Geneva: WIPO; 2011. Available at: http://www.wipo.int/export/sites/www/policy/en/global_health/pdf/report_influenza_2011.pdf

[35] Cavicchi JR, Kowalski SP, Pflugh DL, Barton J, Janovetz J. Patent landscape of influenza A virus Prophylactic vaccines and related technologies. [place unknown]: Franklin Pierce Center for Intellectual Property; 2013. Available at: http://www.wipo.int/export/sites/www/policy/en/global_health/pdf/report_influenza_2011.pdf

[36] Article 27, TRIPS

[37] Article 30, TRIPS

[38] Directive *98/44/EC (1998)*

[39] *Cancer Voices Australia v Myriad Genetics* [2013] FCA 65

[40] *Diamond v. Chakrabarty* [1980] 447 U.S. 303

[41] Resnik DB. The Morality of Human Gene Patents. Kennedy Institute of Ethics Journal. 1997;7(1):43–61.

[42] Drahos P. Biotechnology Patents, Markets and Morality. European Intellectual Property Review. 1999;21.

[43] Kevles D, Berkowitz A. The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics. Brooklyn Law Review. 2001;67.

[44] Eisenberg RS. How Can You Patent Genes? American Journal of Bioethics. 2002;2(3):3–11.

[45] Palombi L. Gene cartels: biotech patents in the age of free trade. Northampton, MA: Edward Elgar; 2009.

[46] Freedom to operate is the ability to proceed with the commercialisation of a new product or process with a minimal risk of infringing on the intellectual property rights of others in the field.
[47] WIPO. Patent issues related to influenza viruses and their genes. Geneva: WIPO; 2007. Available at: http://www.wipo.int/export/sites/www/policy/es/global_health/pdf/influenza.pdf
[48] Novavix, 'Swine-Origin Influenza A (H1N1) Virus-Like Particles And Methods Of Use Thereof' WO/2010/148386
[49] The United States Of America, As Represented By The Secretary, Department Of Health And Human Services 'Influenza DNA Vaccination And Methods Of Use Thereof' WO/2009/092038
[50] 'an anticommons is when 'the number of patents in an area of research or manufacturing becomes so dense, that it restricts innovation in the field, due a lack of freedom to operate for manufacturers' - Heller MA. Can patents deter innovation? The Anticommons in biomedical research. Science. 1998 May 1;280(5364):698–701.
[51] Article 30, TRIPS
[52] Lemley MA, Shapiro C. A simple approach to setting reasonable royalties for standard-essential patents. Berkley Technology Law Journal. 2013;28:1135.
[53] Friede M. IP parameters to vaccines. Geneva: WHO; 2004. Available at: http://www.who.int/intellectualproperty/events/en/WHO-Friede.pdf?ua=1
[54] WTO, WHO & WIPO. Technical Symposium: Access to Medicine, Patent Information and Freedom to Operate. Geneva: WTO; 2011.
Available at: https://www.wto.org/english/news_e/news11_e/trip_18feb11_summary_e.pdf
[55] WHO. Observations on Vaccine Production Technologies and Factors Potentially Influencing Pandemic Influenza Vaccine Choices in Developing Countries: a discussion paper. Geneva: WHO; 2009. Available at: https://file.wikileaks.org/file/pandemic-vaccine-options-2009.pdf.
[56] Khazeni N. Effectiveness and Cost-Effectiveness of Vaccination Against Pandemic Influenza (H1N1) 2009. Annals of Internal Medicine. 2009;151(12).
[57] Neuzil KM. Pandemic influenza vaccine policy — considering the early evidence. New England Journal of Medicine. 2009 Dec 17;361(25):59.
[58] WHO. Report of the WHO pandemic influenza A(H1N1) vaccine deployment initiative. Geneva: WHO; 2012. Available at: http://www.who.int/influenza_vaccines_plan/resources/h1n1_deployment_report.pdf
[59] WHO. Main operational lessons learnt from the WHO pandemic influenza A(H1N1) vaccine deployment initiative. Geneva: WHO; 2011. Available at: http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiaitve_moll.pdf
[60] Pécoul B. Access to Essential Drugs in Poor Countries: A Lost Battle? JAMA. 1999;281(4).

[61] Flynn S, Hollis A, Palmedo M. An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries. The Journal of Law, Medicine & Ethics. 2009;37(2):184–208.

[62] Calabresi G, Melamed DA. Property Rules, Liability Rules, and Inalienability: One View of the Cathedral. Harvard Law Review. 1972;85(6) argues that this right to exclude in order to maintain a monopoly is indicative of patent law being akin to property law in the traditional sense.

[64] Full House Committee on Oversight and Government Reform. [place unknown: publisher unknown]. Developments in the prescription drug market: oversight: Hearing of February 4 2016; 2016 Feb 4 [cited 2017 Jan 24]. Available at: https://oversight.house.gov/hearing/developments-in-the-prescription-drug-market-oversight/.

[65] Walters J. Drug company boss Martin Shkreli refuses to testify to congress. The Guardian. 2016 Nov 11 [cited 2017 Jan 24]. Available at: http://www.theguardian.com/business/2016/feb/04/martin-shkreli-refuses-to-testify-congress-drug-daraprim.

[66] Pollack A. Drug goes from $13.50 a tablet to $750, overnight. Business Day. 2015 Oct 4 [cited 2017 Jan 24]. Available at: http://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html?_r=0.

[67] Charles Baugh, ‘Salt composition and process for making same.’ Available at: https://patents.google.com/patent/US3048525A/en?q=pyrimethamine&before=filing:19600101.

[68] A patent thicket is defined as ‘a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology.

[69] WHA. Resolution WHA61.15, Sixty-First World Health Assembly. 2008

[70] WHA. Resolution WHA65.17, Sixty-Fifth World Health Assembly. 2012

[71] WHO. Report of the second WHO consultation on the global action plan for influenza vaccines (GAP). Geneva: WHO; 2012. Available at: http://apps.who.int/iris/bitstream/10665/44794/1/9789241564410_eng.pdf

[72] Kane E. Achieving clinical equality in an influenza pandemic: Patent realities. Seton Hall law review. 2009;39(4):1137.

[73] A key technology in improving influenza vaccine manufacturing. In essence, reverse genetics manufacturing allows the viral components of a vaccine to be grown in higher yields, under more stable conditions than the traditional egg-based development of viral samples.

WHO. WHO guidance on development of influenza vaccine reference viruses by reverse genetics department of communicable disease surveillance and response global influenza Programme. Geneva: WHO; 2005. Available at: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_6.pdf

[74] There are generally regarded to be four patent portfolios associated with the reverse genetics technology. (WO 91/03552) (WO 00/60050) (WO 01/83794) (U.S. Patent No. 6,544,785)
[75] MedImmune. MedImmune advancing science for better health - annual report. [place unknown]: Medimmune; 2006. Available at:
http://media.corporate-ir.net/media_files/irol/83/83037/Annual%20Reports/AR2005.pdf>
[76] MedImmune, 'Statement from Medimmune, Inc. Regarding Reverse Genetics Technology' reported at Knobler S, Knobler SL, Mack A, Lemon SM. The threat of pandemic influenza: Are we ready? Workshop summary. Mahmoud AAF, editor. Washington, D.C.: National Academies Press; 2005 Mar 9.
[77] Drahos uses this term to refer to public goods
(78) Drahos P. A philosophy of intellectual property. Aldershot: Dartmouth Publishing Co; 1996 Nov 14.
[79] Drahos P, Braithwaite J. Information feudalism: Who owns the knowledge economy? New York: Distributed by W.W. Norton & Co.; 2003 May 1.
[80] WHO. Global pandemic influenza action plan to increase vaccine supply: Immunization, vaccines and Biologicals (2006-2008). Geneva: WHO; 2008.
[81] as quoted at: Dubos RJ. Louis Pasteur, free lance of science. 2nd ed. New York, NY: Da Capo Press; 1986 Mar 1.