Background paper for WHO workshop

Intellectual Property Rights and Vaccines in Developing countries

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Christopher Garrison
Consultant Legal Advisor to WHO
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This paper was prepared for the purpose of the meeting. The views expressed therein should not be taken as representing any policy position or statement of the World Health Organization (WHO).

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EXECUTIVE SUMMARY

This is a background paper for the forthcoming WHO workshop on IP and vaccines and is intended to provide an outline of some of the relevant issues for consideration as well as suggested options and directions to pursue.

The issues of access to technologies, research and development (R&D) and technology transfer are intimately linked. How R&D is carried out will very likely determine the constraints on access to, and technology transfer of the products of that R&D. The following sections therefore examine the linked issues of access to IP protected technologies, the stimulation or otherwise of R&D and technology transfer by IP and the context in which all three operate.

Intellectual property and access to IP protected vaccine technologies

The TRIPS Agreement today provides for a number of intellectual property rights that are relevant to vaccines, including for example:

- Patents – there are now a wide range of vaccine related inventions that may now be patented ranging from 'upstream' research related inventions to 'downstream' development, production and delivery related inventions.

- Undisclosed information – 'Know-how' perhaps plays a larger role in vaccine production than in medicines and may be regarded as including both certain sorts of 'undisclosed information' ('trade secrets') and more general knowledge – to a greater or lesser extent there seems to exist a know-how gap between e.g. OECD vaccine manufacturers and 'emerging' vaccine manufacturers.

- Undisclosed test or other data – this is a subset of 'undisclosed information' and is important in the field of medicines in terms of the use of 'bio-equivalence' to accelerate regulatory approval – it may not be so important for vaccines in these terms if each manufacturer has to carry out their own clinical trials.

Intellectual property monopolies are not absolute. Patent monopolies are for example limited in terms of scope (what is, and is not, prevented by the patent), in terms of geographical extent (they are only granted on a country-by-country or occasionally regional basis) and in terms of time (they have a (minimum) lifetime of twenty years). Pricing decisions, within certain limits, are in the hands of the patent owner. If a new vaccine is priced in an affordable fashion then access to that vaccine will be commensurately less difficult. Nevertheless, patents are, by their very design, intended to permit a price to be struck which could not be supported in usual conditions of competition. Due to the limits of patent monopolies, competition to a patented vaccine may arise for example from:

- Another vaccine which achieves the same or similar result but through the use of a different technique. Compare for example a plasma derived vaccine and a recombinant vaccine. How often is a patented vaccine likely to have an effective competitor?

- A version of the vaccine made in a country where the patent is not in force – although this vaccine will not be able to be sold in any countries where the patent is in force. The TRIPS Agreement represents a radical change in this respect – all WTO Members (except Least Developed Country Members) have to permit patents for pharmaceutical products, including vaccines, by 1st January 2005. Will competition from emerging manufacturers therefore be suppressed? Will global vaccine patent

monopolies become the norm in the future? This can be expected to have a significant impact on the price of patented vaccines.

- A version of the vaccine made after the patent has expired. In terms of the public health needs of the developing world it cannot be acceptable to wait for the patent to expire. There are mechanisms available in theory under the TRIPS Agreement to enable competition during the lifetime of the patent, e.g. compulsory licensing, but factors such as know-how may impact their effectiveness.

The hypothesis has been advanced that intellectual property does not significantly impact access to vaccines through for example raising prices. The argument is made that in for example the case of the recombinant DNA Hepatitis B vaccines, the maximum patent licence royalty rate was 15%. However, since a patent owner and licensee are in effect in a managed relationship, it is likely that the more significant contribution to price will arise from the fact that the patented vaccine may not experience any true competition. In fact it appears that the recombinant DNA Hepatitis B vaccine experienced price competition from a plasma derived Hepatitis B vaccine, and so cannot seemingly be relied upon as a good example of how a "worst case" patent monopoly will impact vaccine price.

Notwithstanding the "WTO Doha Declaration on TRIPS and Public Health", new, bilateral and regional Free Trade Agreements are being agreed that bind the parties to "TRIPS-plus" protection (higher standards than the TRIPS Agreement requires), such as:

- Longer patent lifetimes to make up for time lost in the regulatory approval process

- Linking patent issues into the regulatory approval process

Although the full impact of the TRIPS Agreement on public health in the developing world is not yet known, these supplementary agreements will further strengthen intellectual property right monopolies.

The UK Commission on Intellectual Property Rights (CIPR) expressed concern at the reduction of competition that the TRIPS Agreement will likely bring and called for ways to be found, within the patent system and without, to generate the necessary competitive environment to help offset the adverse price effects of patents on developing country consumers.

Mechanisms that have been used to facilitate access to patented vaccines include:

- Tiered pricing – this is a traditional mechanism for facilitating access to vaccines. This is in part because 'parallel importation' tends not to take place given the 'cold chain' nature of vaccine distribution. However the phenomenon of 'schedule divergence', where different vaccine products are now provided to segments of markets that used to share a single vaccine product, may threaten the use of tiered pricing in the future.

- Bulk purchasing – this is also a traditional mechanism for facilitating access to vaccines due to the importance of vaccine production scale issues and the need to predict demand. Procurement processes of the sort that were so successful in reducing the price of the Hepatitis B vaccine (the Hepatitis B Task Force sealed bid tender) may face difficulty (post 1st January 2005) as global vaccine patent monopolies tend to increase the likelihood of encountering single suppliers.

- Voluntary licensing – voluntary licensing may take a number of different forms starting from a 'bare' patent licence, through permitting the licensee to carry out a certain stage of the vaccine production process, to a full technology transfer to put the licensee in the same position as the patent owner. Business model considerations will apply and as noted above, it cannot be expected that voluntary licensing will necessarily result in the same reductions in price that would appear in a truly competitive situation.

- Compulsory licensing –a 'compulsory' licence can be granted where for example the patent holder has abused their monopoly or where it is otherwise in the public interest. Whether or not the necessary know-how is possessed by a potential compulsory licensee will impact the effectiveness of compulsory licensing.

Which of these, or other mechanisms, is going to play a role in facilitating access to patented vaccines in the future?

IP and R&D for vaccines

How R&D is carried out will to a great extent determines access to the products of that R&D. The predominant mode of (private sector) R&D incentivisation is through intellectual property and the TRIPS Agreement and consequently the section above deals with access to IP protected products, and the section below deals with IP framed technology transfer. It is not possible to divorce the effectiveness of the intellectual property in stimulating R&D from the viability of the underlying market for the product of that R&D. There are a number of possibilities for different health R&D approaches:

- The possibility of a patent monopoly in a rich market, promising profit, can be expected to encourage private sector R&D. The possibility of a patent monopoly in a poor or non-existent market, promising little or no profit, can be expected to encourage little or no private sector R&D, as the UK Commission on Intellectual Property Rights (CIPR) found. The private sector R&D programmes that are presently observed also support this thinking. By way of confirmation of this problem, measures supplementary to intellectual property are being discussed and/or provided to try to incentivise the private sector further.

- The public sector carries out a lot of basic research. The public sector lacks the skills to develop and produce vaccines, it having traditionally been the competence of the private sector. There is now discussion of the possibility of a new public sector institution to provide vaccine development and production skills in cases where the private sector will not or cannot supply those skills (for example due to opportunity costs). The impact of the Bayh-Dole Act has generated some concern about moving intellectual property protection 'upstream' into basic research.

- Public Private Partnerships (PPPs) present the possibility of bringing together the strengths of both sectors. Intellectual property agreements are often the heart of PPPs in terms of tying together a non-viable market with a viable market. The PPP model is still perhaps in an investigatory phase. There have been interesting IP related developments with at least two PPPs: the International AIDS Vaccine Initiative (and perhaps the "HIV/AIDS vaccine enterprise") and the Meningitis Vaccine Project.

Where too many, or overly broad or strong intellectual property rights are granted, they can act as a dis-incentive to carry out R&D, rather than as an incentive.

IP, technology transfer and local production of vaccines

The TRIPS Agreement has provisions to encourage technology transfer but cannot, in the ordinary course of events, compel it.

Technology transfer may take place in a number of different forms:

- Technology transfer in the private sector is business model based e.g. to lower costs and therefore has supplementary requirements other than IP considerations before it is likely to take place. There is perhaps a tension between OECD and emerging vaccine suppliers in terms of strategic cooperation versus strategic competition.

- Contract research and technology transfer could perhaps be utilised to remedy know-how gaps on the part of emerging producers, as for example proposed in the Meningitis Vaccine Project model.

- There are also perhaps possibilities for e.g. non-commercial technology transfer in the public sector

A vital question in terms of vaccine supply is that of "local production"– some consider that this is essential, to enable each country or region to master the necessary technologies, but others believe that it is undesirable, e.g. from a quality or economies of scale point of view, and believe that importation from global producers is a better model.

Options and directions to consider

A variety of suggested issues for further study are raised, to guide discussion and focus further research and to ground an evidence based WHO perspective and policy on IP and vaccines. A few key issues are:

- How best to understand the influencing factors in the vaccine access problem in terms of IP rights such as patents and undisclosed information (including trade secrets and undisclosed clinical trial or other data). Such a characterisation should permit better preparation and more effective action to address IP related vaccine access problems.

- The impact of IP on the stimulation of R&D, in order to better understand where IP is likely to stimulate R&D and where it is not. In situations where IP cannot be expected to stimulate R&D by itself, various other R&D possibilities may be studied including additional private sector incentives, public sector possibilities and public-private partnerships. Further consideration also needs to be given to whether there is a danger that in some circumstances IP could act as a disincentive to, or otherwise hamper, R&D

- The impact of IP on the stimulation of technology transfer, in order to better understand what can be expected from IP-led private sector technology transfer. In situations where IP cannot be expected to stimulate technology transfer by itself, various other technology transfer possibilities may be studied including public sector possibilities and public-private partnership models, perhaps based on contract research and development. Another important related issue is that of the arguments for and against "local production".

1. Introduction to this paper

Following World Health Assembly resolution WHA56.27, the World Health Organisation has recently established a Commission on Intellectual Property, Innovation and Public Health, which under the terms of the WHO Director-General's note "Intellectual property rights, innovation and public health: terms of reference for review group"[1] will be investigating the following issues:

- Summarize the existing evidence on the prevalence of diseases of public health importance with an emphasis on those that particularly affect poor people and their social and economic impact

- Review the volume and distribution of existing research, development and innovation efforts directed at these diseases

- Consider the importance and effectiveness of intellectual property regimes and other incentive and funding mechanisms in stimulating research and the creation of new medicines and other products against these diseases

- Analyse proposals for improvements to the current incentive and funding regimes, including intellectual property rights, designed to stimulate the creation of new medicines and other products, and facilitate access to them

- Produce concrete proposals for action by national and international stakeholders

The WHO/ Immunizations, Vaccines and Biologicals (IVB) department is presently conducting a process of review of intellectual property and vaccine positions in the run-up to the forthcoming Strategic Advisory Group of Experts (SAGE) meeting.

Approaches to the impact of intellectual property on vaccines have been expressed in documents such as the following: "The World Trade Organisation: What is it and why is it relevant to vaccines?", prepared by the Global Programme for Vaccines and Immunization of the WHO and the Children's Vaccine Initiative (CVI)[2], "Intellectual property protection: Its role and benefits" prepared by the CVI[3] (referred to in this paper as the "CVI" document) and "WTO Agreements & Public Health, A joint study by the WHO and the WTO Secretariat"[4] (referred to in this paper as the "WHO/WTO document").

The forthcoming workshop aims to examine the impact of the global intellectual property rights regime on vaccines from a contemporary perspective. In particular the workshop seeks:

- To identify the role of intellectual property in affecting access to vaccines in developing countries.

- To identify directions and options for ensuring an appropriate balance between protection of innovation and access to most needed vaccines in developing countries.

- To identify what could be the WHO role with regard to vaccine related IPRs.

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[1] See EB113/INF.DOC/1, "http://www.who.int/gb/EB_WHA/PDF/EB113/eeb113id1.pdf
[2] Submitted to the SAGE meeting of 11-13 June 1997 in Geneva, reference GPV/SAGE.97/WP.14
[3] reference CVI/99.04
[4] 2002, the document does not seem to bear any identification number.

- To provide an input on the above issues to the commission on IPR, Innovation and Public Health.

This paper is intended to provide an outline of some of the relevant issues for consideration at the workshop[5]. The issues of access, research and development (R&D) and technology transfer are intimately linked. How R&D is carried out will very likely determine constraints on access to and technology transfer of the products of the R&D. If, for example, R&D is stimulated by IP then the product of that R&D is likely to be IP protected. The paper is therefore divided into sections examining access to IP protected technologies, the stimulation or otherwise of R&D and technology transfer by IP and the context in which all three operate.

[5]. The author would like to thank Mr Miloud Kaddar, Mr Michel Zaffran (WHO/IVB/ATT) and Mr Patrick Gaulé, consultant ATT, for their assistance, comments and suggestions in preparing this paper. The author would also like to thank Dr Julie Milstien, Professor Richard Mahoney and Dr Warran Kaplan for their comments and suggestions. Nevertheless the paper should not be taken as representing any policy position or statement of the WHO or any of the individuals thanked.

2. Introduction to Intellectual Property and Vaccines

In the last few years, there has been a substantial debate about how intellectual property impacts medicines and in particular how the TRIPS Agreement impacts access to medicines in the developing world. Vaccines are different from medicines in a number of important respects however (at least from the small molecule 'pill' medicines if not the newer 'biotech' medicines). The issues raised in the access to medicines debate may therefore apply to a greater or lesser extent for vaccines, depending on these differences. This section examines a few of the different forms of intellectual property rights that are relevant in the context of vaccines and outlines the impact of some of the differences between vaccines and medicines.

"Intellectual property" is a term which is used to bring together a number of different concepts. Patents, trademarks, copyright, designs and undisclosed information are some well known examples of intellectual property provided for under the TRIPS Agreement[6]. Patents and undisclosed information are both forms of intellectual property that could be directly relevant to vaccines. Patents (Articles 27-38 TRIPS) protect inventions. A broad class of 'undisclosed information' (Article 39 TRIPS) potentially includes both e.g. information relating to vaccine production processes and e.g. aspects of vaccine clinical trial or other test data. Other intellectual property rights may also impact vaccines, such as trade mark or 'brand' protection, but they are not discussed further here.

2.1 Patents

A set of rules governing patents is provided in the TRIPS Agreement, some of which are now discussed as a basis for subsequent discussion on the impact of patents on vaccine access, R&D and technology transfer.

A patent shall be granted for an invention so long as it is demonstrated that the invention passes certain necessary tests such as being "new" and involving an "inventive step" (TRIPS Art 27.1). A new vaccine may include a number of different inventions, each of which may be separately patented, and may therefore have a 'portfolio' of associated patents. In general, there has been a remarkable increase in the number of separate inventions that are permitted to be patented in the field of biotechnology, which obviously has important consequences for the patent protection of new vaccines[7]. Relevant patented inventions might include products (including e.g. a micro-organism in a living but attenuated state, (recombinant) antigens and antibodies, an adjuvant or a vaccine delivery device) and processes (e.g. relating to a method or steps in a method for producing a vaccine).

Applications for patents are published and must disclose to the public how to carry out the invention (TRIPS Art 29.1). A patent application will also disclose what the limits of the monopoly applied for are, the patent 'claims', based on the description of the invention in the patent application. Patents are, or are supposed to be, private rights as the preamble to the TRIPS Agreement makes clear and as a result it should be down to the patent holder to sue a third party if they "infringe" the patent holders rights. These rights include the rights to exclude third parties from e.g. making, using or selling the claimed invention (TRIPS Art 28.1). A patent holder may agree to licence their patent to a third party, i.e. give them permission to do something which would otherwise have been a patent "infringement" or may assign their patent outright (TRIPS Art 28.2).

[6] For an in-depth introduction see, for example, "Intellectual Property Rights in the WTO and Developing Countries", Jayashree Watal, Kluwer Law International, 2001.
[7] For an introduction, see for example "Biotechnological Inventions", Chapter 13 in "Patents for Chemicals, Pharmaceuticals and Biotechnology", Grubb, Oxford University Press, 1999.

So long as the patent holder keeps paying the patent renewal fees, patents shall last a minimum of 20 years from the date on which the patent application was first filed (TRIPS Art 33). However, since the process of regulatory approval of a vaccine takes a number of years, the effective length of patent life protecting a commercial product will very likely be shorter.

The monopoly provided by a patent is not absolute. **The scope of a patent monopoly is intrinsically limited in terms of subject matter, geographical extent and time**, as is discussed further below[8]. There are certain acts which can be defined to be exceptions to the patent monopoly e.g. within certain limits acts carried out for the purposes of research (TRIPS Art 30). Also, if a patent holder abuses their patent monopoly and/or it is in the public interest a "compulsory licence" may be granted to permit a third party to carry out any acts that the patent holder could normally have forbidden (TRIPS Art 31). If a patent monopoly turns out to have been wrongly granted then it can be revoked (see e.g. TRIPS Art 32).

2.2 Know-How

It is possible to draw a distinction between a general definition of know-how, for example "Technical expertise; practical ability or invention"[9] and a more specific form of confidential know-how or trade secret. Article 39 of the TRIPS Agreement protects this latter type of "undisclosed information" as an intellectual property right, although it is somewhat misleading to think of it in 'property' terms. It is certainly very different in nature from the intellectual property rights that can be applied for and 'registered' (for example a patent or a trademark). Certain conditions are set in Art 39.2 TRIPS for what can be regarded as undisclosed information of this sort[10]. Legal powers are provided to the owner of this undisclosed information such that if someone acquires it in a improper fashion (e.g. they steal it), the owner of that information should have the power under the national law implementation of TRIPS to stop that other person from using it. The scope of this provision goes wider than just technical information and can include e.g. commercial information such as customer lists.

Vaccines are relatively complex biological products and the vaccine production process is commensurately difficult (compared perhaps to "pill" medicine production). **"Know-how" is reported to play an important role in the process of vaccine production[11]**. The WHO/WTO document recognises the importance of "know-how" in the following terms (box 15, p97):

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[8] A further effective limitation may arise from the fact that patents grant the right to prevent others from using the patent owners invention but they do not guarantee that patent owners can carry out the their own invention. If, for example, a patent holder has a patent for a 'specific' invention, it may be that somebody else has a 'general' patent which the patent holder would need to get permission to use, if they wanted to use their own invention.

[9] New Shorter Oxford English Dictionary

[10] Art 39.2 TRIPS Agreement provides that:

"Natural and legal persons shall have the possibility of preventing information lawfully within their control from being disclosed to, acquired by, or used by others without their consent in a manner contrary to honest commercial practices [footnote not included] so long as such information:

(a) is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question;
(b) has commercial value because it is secret; and
(c) Has been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret."

[11] Milstien, J and Widdus, R "Facilitating Access to Vaccines: An Overview of Legal and Political Issues" Pharm Dev Regul 2003; 1 (2) : 101-116

> "A significant amount of "know-how" is needed in order to produce a vaccine. This know-how is not communicated through process or product patents. For this reason, compulsory licensing is unlikely to be an effective means of transferring vaccine production capacity."

Know-how as used in the sense of the WHO/WTO document could presumably include both the specific legal form of confidential know-how or trade secret protected under the TRIPS Agreement and the more general form. The know-how may include specific technical insights or it may reside in the aggregation of many years of experience in running vaccine production processes. It may be formally documented or it may perhaps be rather more difficult to pin down. It may be kept intentionally secret or it may not. Biological material itself may be treated as a "trade secret" and if it is to be shared between different parties, for example in the case of a given cell line, a Material Transfer Agreement (MTA) may be concluded, to ensure the appropriate confidentiality conditions are observed.

However it is generated though, and whether or not it is deliberately kept confidential, a **key question is whether or not this know-how is available to third parties**. If the necessary know-how to produce a given vaccine is available to a third party then, absent other relevant barriers, that third party should be able to produce the vaccine. If the necessary know-how is not available to the third party then, absent finding it out for themselves or contracting with someone else who has the know-how or could develop it, that third party will likely not be able to find a way to produce the vaccine[12]. It is for this reason that the WHO/WTO documents notes the link to compulsory licensing (of patents) although it is arguably not so much about technology transfer *per se* as simply being able to carry out production.

2.3 Undisclosed test data

'Undisclosed test or other data' relates to even more narrow concept than 'trade secrets'. It is a relatively newly created type of intellectual property right and can be seen as protecting investment rather than innovation or inventiveness per se.

Before a pharmaceutical product can be marketed, it has to be approved (licensed) by the regulatory authorities, and this involves among other things carrying out clinical trials. Given the expense involved in generating the clinical trial and other data needed for regulatory approval, the argument was made that the 'originator' should have their 'investment' protected so that others cannot 'free-ride' upon it. In respect of "undisclosed test or other data", Article 39.3 of the TRIPS Agreement therefore binds members to protect such data against 'unfair commercial use' and 'disclosure' (except where necessary to protect the public). There is still a great deal of debate over how to implement the 'unfair commercial use' provision in national law however. One interpretation favours the holder of data, and calls for a period of exclusivity, typically 5 years, during which time a third party cannot rely on the originator data by gaining approval after demonstrating that their product is bio-

[12] There is perhaps the issue of whether or not 'undisclosed information' could be the subject of an appropriate form of compulsory licence. A previous draft of the TRIPS Agreement (July 23rd, 1990, W/76) contained a provision that "There shall be no compulsory licensing of proprietary information", but this provision was not included in the TRIPS Agreement as adopted. The issue of mandatory disclosure of such information to competitors does seemingly arise in the context of competition law / antitrust cases, such as the recent European Commission Microsoft case. One significant issue to bear in mind though is that presumably the owner of the proprietary information can be compelled to comply in such cases, brought in wealthy countries, as they want to remain in business in those markets; the degree to which they could be obliged to transfer their proprietary information to competitors in a developing country is perhaps not so clear. Companies are evidently being *persuaded* to transfer such information to some developing countries, given the lure of the market opportunity, see e.g. "China Sets High Price To Gain Market Entry: Advanced Technology", Wall Street Journal Europe, Friday 27th, 2004.

equivalent (or "therapeutically equivalent"). Another interpretation, favouring the speeding of competing products entering the market, permits the registration of third party products on showing that they were bio-equivalent.

The protection of 'undisclosed test or other data' may likely have less impact in the field of vaccines than medicines however. Given the nature of small-molecule 'pill' medicines it is possible to utilise bio-equivalence techniques to determine with certainty that a generic medicine is fully equivalent to an originator medicine. For more complex biological constructs such as vaccines (or the newer 'biotech' medicines) such a bio-equivalence comparison is not yet possible. Given the sensitivity of vaccine products to the specifics of the production process, it seems instead to be the case that each vaccine manufacturer has to engage in clinical trials for their own product and obtain licensure on the basis of their own unique data.

In the field of medicines, the data exclusivity interpretation of the TRIPS obligation will slow down competition by generic medicines by, for example 5 years. If vaccine manufacturers cannot use the avenue of 'bio-equivalence' to obtain licensure, then this impact may not be felt; the 'long way round' of carrying out clinical trials can be expected to slow the appearance (and raise the price) of 'generic' vaccines in every case. This situation may change. The US Food and Drug Administration is now beginning to work on the issue of what can be done to speed approval of "generic" biotechnology derived products, "We are concerned about finding safe ways to lower drug costs for Americans…If we can find a safe path to generic or follow-on products for biologics, that can be an important step"[13].

2.4 Vaccine delivery devices[14]

IP protection of vaccine delivery devices is also very important having regard to the delivery of the end product vaccine. Given that the vaccine delivery devices will have very different characteristics from vaccines *per se*, e.g. they may be mechanical devices rather than biological products, IP issues will have a different impact. It can be expected that patents will still be very relevant but that considerations of know-how may have less importance. There is "significant IP on delivery systems such as nasal delivery sprays, patches for applying drugs through the skin, and ballistic delivery systems [and] when combined with a vaccine (i.e. the licensed vaccine is contained within or delivered via a particular device) the product is covered by both the IP on the vaccine component, the IP on the delivery device and often IP on the vaccine delivered by a device with particular characteristics"[15].

2.5 TRIPS, Doha and TRIPS plus

Much of the access to medicines debate has been about the freedom available to WTO Members to interpret and implement the TRIPS Agreement. On 14th November 2001, all WTO Members agreed the WTO Doha Declaration on TRIPS and Public Health. The Doha Declaration recognises the "gravity of the public health problems afflicting many developing and least developed countries", recognises that "intellectual property protection is important for the development of new medicines" but simultaneously recognizes the "concerns about its effects on prices". The center-piece of the Doha Declaration (paragraph 4) states that:

> We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our

[13] FDA Commissioner Mark McClellan quoted in "US is Setting a Path for Biotech Generics", The Wall Street Journal Europe, February 18th 2004.
[14] Note e.g. "Technologies For Vaccine Delivery In The 21st Century: A White Paper of WHO, UNICEF, USAID and PATH".
[15] Martin Friede, WHO, personal communication.

> commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all. In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.

Compulsory licensing is one of these flexibilities, as explicitly noted by the Doha Declaration, although an outstanding legal problem with compulsory licensing under the TRIPS Agreement could not be solved in Doha – that of how to enable compulsory licensing (or any other mechanism) that would permit production of pharmaceutical products for export to countries "with insufficient or no manufacturing capacities in the pharmaceutical sector"[16]. On August 20th 2003, all WTO Members agreed on a new legal mechanism to solve this outstanding problem. It would appear that vaccines are included within the scope of this new mechanism[17].

Notwithstanding all of the above, it is clear that certain WTO Members, the United States being the most prominent example of which, do not regard the TRIPS Agreement (and in particular the TRIPS Agreement as understood after the Doha Declaration) as a sufficient basis for satisfactory intellectual property protection. It is not clear that this position is motivated by an evidence-based approach to improving public health in the developing world. A number of recently agreed bilateral or regional 'Free Trade Agreements' (FTAs) initiated by the United States bind the relevant parties to more restrictive intellectual property provisions than called for by the TRIPS Agreement ("TRIPS plus" provisions)[18]. The TRIPS plus provisions are often simply the ones that the United States or other OECD *demandeurs* called for in the TRIPS negotiations but which were rejected in the final TRIPS Agreement text. Examples of recent FTAs are CAFTA (United States and Central American States) and the United States – Australia and United States - Morocco FTAs. It is very likely that the United States intends that these agreements should be models for further FTA negotiations for example those with the South African Customs Union[19]. It is also very likely that if enough bilateral or regional partners are persuaded to adopt TRIPS plus standards, there may be pressure to return to the WTO to seek to have these TRIPS plus standards approved as the new basic multilateral standards.

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[16] In fact the discussion focused on the TRIPS Agreement requiring that the authorisation of the compulsory licence be made "predominantly for the supply of the domestic market" (TRIPS Art 31(f)). In other words an authorisation could already be given under TRIPS in respect of a non-predominant portion of the production (e.g. 1-49%) and what had to be found was a way to extend that under the circumstances discussed to include a predominant portion of the production (51%-100%).

[17] Although the Japanese government reportedly asked for the word "vaccines" to be removed from a draft of the text this was apparently not regarded by other negotiators as an exclusion of vaccines from the mechanism. The definition of "pharmaceutical product" in the text is apparently regarded as sufficiently broad to include vaccines, see e.g. "The WTO Decision on Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health", Vandoren and Van Eeckhaute (EC negotiators), Journal of World Intellectual Property, Vol.6, No.6, November 2003.

[18] Subject to the FTAs entering into force.

[19] The United States Trade Representative takes formal input from US industry on the content of the FTAs – the recently published "IFAC-3" comments on the Australian and Central American FTAs give an insight into their thinking (see e.g. http://www.ustr.gov/new/fta/Australia/advisor/ifac03.pdf , italics added): "IFAC-3 is particularly gratified that AFTA preserves these strong precedents set forth in these other agreements and now, with high-level agreements with both *small developing countries* in the CAFTA and a strong and mature developed country like Australia, it will prove much easier to *convince* future FTA countries that strong intellectual property protection is in the interest of all countries *regardless of their economic circumstances.* Accordingly, IFAC-3 urges the U.S. government to keep this in mind when negotiating with countries such as those in the SACU, which have much to gain from maintaining the high levels of protection negotiated to date". "SACU" is the South African Customs Union.

Examples of such TRIPS plus provisions include the following.

> Patent life is extended beyond 20 years "to compensate the patent owner for unreasonable curtailment of the effective patent term as a result of the marketing approval process" (CAFTA 15.10(2))
>
> Where a pharmaceutical product is covered by a patent, the marketing approval process must prevent persons other than the patent owner from marketing a product during the lifetime of the patent unless the patent owner consents or acquiesces (CAFTA 15.10(3)(a))

So, in any developing country that has agreed to such terms, the patent lifetime may be extended by a number of years beyond the usual twenty and the marketing approval process will ensure that any products considered to be covered by such a patent during the extended lifetime are denied marketing approval. The patent owner will benefit from a longer patent monopoly and the government of the country will, in effect, enforce the patent without the patent owner having to be involved (as TRIPS would usually require). This will have a significant impact on the countries access to affordable pharmaceutical products. If the country were wishing to procure pharmaceutical products for example, under this regime only the patent owner will be able to supply, or at least only anyone with their permission. Unless steps such as the granting of a compulsory licence are taken, the price competition associated with open tenders and generic competition will be prevented until the now-longer patent monopoly has expired (see box on procurement below in section 3.7.2)

3. Access to IP protected vaccine technologies

In many ways it is artificial to draw a distinction between access to new vaccines and R&D for vaccines in that how the R&D is carried out will likely have a significant impact on access to the final product. The following section looks at access to end-product vaccines which have been developed in such a way that they are protected by intellectual property rights. The issue of access to the necessary inputs in the early stages of R&D is also clearly a concern but will be addressed in the R&D section below (see section 4.7 below).

3.1 The Access problem and IP

The desperate plight of many of the world's poorest people lacking access to essential medicines and vaccines is absolutely clear. It is self-evident that the high price of a new medicine or vaccine will have a strong impact on its availability in the developing world. In turn, there can be many factors involved in a high end price, of which patent protection might be only one. Nevertheless, given that patents are intended to provide market monopoly rights, they are obviously a prime possible concern.

The recent WHO/UNICEF/World Bank publication, "State of the World's Vaccines and Immunization"[20] addresses the access gap in vaccines. It is indicated that (page 7) "[T]he divide in access to vaccines between wealthy and poorer countries has widened even further over the past two decades, as new life saving vaccines have become available – at prices that most low-income countries could not afford". The reason for this lack of affordability is said to spring from a number of sources including lack of funds, lack of adequate infrastructure and lack of adequate disease burden surveillance. This latter factor means that, because vaccine production is highly scale sensitive, manufacturers will tend not to devote more capacity to the necessary production than they need at the outset. This will cause difficulty both in the higher price resulting from smaller production runs and the problems of increasing

[20] "State of the World's Vaccines and Immunization", WHO, 2002

scale at a later date. As far as the setting of the price is concerned, the following is said (page 9):

> "In order to recoup these [vaccine development] costs and make a profit, vaccine manufacturers subsequently set a high price for each new vaccine. Exclusive rights to an initial 20-year period following the introduction of the vaccine is protected by patents under the Agreement on Trade Related Aspects of Intellectual Property Rights (also known as the TRIPS Agreement). Patents give the manufacturer exclusive rights to either produce the vaccine themselves or licence production to another manufacturer in return for payment of royalties. Once the patents have expired, other vaccine manufacturers are free to produce the vaccine without payment of royalties. Over time, this leads to competition, which in turn may lead to overcapacity and a willingness to sell at a low profit margin. In the meantime, millions of childrens lives are being lost in developing countries, where governments are unable to afford the new vaccines until the price is reduced, 10-20 years later".

This is a pretty damning indictment[21]. The WHO/WTO document addresses access to patented vaccines in the rather different terms (box 15, p97):

> Does patent protection restrict access to essential vaccines? Until recently there has been about a 15 year time lag between the introduction of a new vaccine in the developed world, and its uptake in developing countries. Clearly, the higher prices of relatively new vaccines are one of the barriers to their adoption, and royalties do contribute to the cost of vaccine production. However WHO experts note that utilization is no greater for off-patent vaccines than for patented vaccines against the same antigen, even where they are equally effective. This has been shown for hepatitis B and acellular pertussis. Furthermore, the contribution of royalties to selling price is generally in the range of zero to six percent. In general, patent protection does not appear to be a major barrier to current vaccine uptake and utilization in developing countries."

It is absolutely clear that there is a significant and unacceptable delay in the introduction of new vaccines to the developing world. It is precisely for this reason that the Global Alliance for Vaccines and Immunization (GAVI) has been set up, not only in terms of long standing problems such as Hepatitis B and Hib vaccines, but also in terms of the new Accelerated Development and Introduction Plans (ADIPs)[22]. There is evidently still some lack of clarity however on the extent to which patents, or other intellectual property rights, play a role in this delay.

A broad-ranging investigation of the impact of IP on access to, in particular medicines, was carried out by the UK Commission on Intellectual Property Rights (CIPR). Their report[23] should be taken as important background material for this paper and workshop process.

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[21] One small correction should perhaps be made though: although patents do last 20 years, this is not from the date of "introduction" of the vaccine, it is from the date of filing for the patent application, which may predate the introduction of the vaccine by a number of years, a notional 10 years being suggested in this document to include all developmental stages from pre-clinical through clinical trials and up to and including registration.

[22] "The Global Alliance for Vaccines and Immunization was formed to harness the strengths and experience of multiple partners in immunization. It is an historic alliance between the private and public sector committed to the mission of saving children's lives and people's health through the widespread use of vaccines." See http://www.vaccinealliance.org

[23] "Integrating Intellectual Property Rights and Development Policy", Commission on Intellectual Property Rights, see http://www.iprcommission.org/

Following on from the introductory section above, it is clear that various intellectual property rights may play a role in access to vaccines, including patents and undisclosed information (including trade secrets and undisclosed test data). Whether or not a trade secret, vaccine production know-how is clearly very important. The following sections examine some of the important aspects of the relationship between patents, know-how, undisclosed information and competition.

3.2 How can competition to a patented product arise?

The full effect of a vaccine patent monopoly might be experienced where a patented vaccine is not subject to any effective competition and, absent other considerations, the patent holder is able to price the vaccine at whatever price they feel would maximise their profit. As noted above however, the scope of a patent monopoly is limited and, depending on the particular limitation in each case, it may be possible for there to exist a competing vaccine product e.g. utilising a different technology to achieve the same or a similar result to that achieved by the patented invention. Clearly the consequences for the vaccine price will be very different if a single patent holder is able to price the vaccine in the absence of any competition from where the patent holder's product has to compete with another product in the market (the possibilities for and effects on competition of granting a voluntary patent licence (and for that matter a compulsory licence) will be discussed below in section 3.7.3). Competition may arise with patented products in at least three different ways.

(a) **Patent monopolies are limited in scope**, so there may be an unpatented (or other patented) product outside the scope of the patent monopoly, which can be substituted for the patented product. In this case the full price effect of the patented product may not occur. It should be noted that it is very much part of the operation of the patent system for third parties to try to "invent around" patents[24]. Patent holders will always try to make their scope of monopoly as wide as possible. However, since the scope is limited there may be other ways to achieve what the patent holder has achieved without falling within the claimed boundaries of the patent monopoly. It is as much part of the job of a patent attorney to assist in this process of inventing around somebody else's patent as it is to secure the widest possible scope of patent monopoly for their client. Indeed some of the spur to carry out invention in the patent system is supposed to come from this activity. The proper scope of patents, i.e. how wide a scope of patent monopoly should the patent applicant be rewarded with based on what they claim to have invented, has therefore always been an important question. The case of the Biogen patent protecting a recombinant Hepatitis B vaccine is noted further below in this section: this patent was determined in court to be overly broad and was therefore revoked. An even more fundamental example is provided by e.g. the overly broad patents that have been granted on gene sequences[25].

(b) **Patent monopolies are also geographically limited**, on a country by country (or occasionally regional[26]) basis. Competition may occur with the patented product in markets where the product is not patented. Competition may also occur with the patented product in markets where the product is patented if the patent holder declines to enforce their patent. There must always exist a tension between what a patent holder wants, i.e. as broad a scope of patent monopoly as possible enforced in as many countries as possible at the lowest possible

[24] It is important to be clear about the difference between e.g. inventing around a patent and obtaining a compulsory licence of a patent as misunderstandings do arise, see e.g. p34, "Moving Beyond the Barriers: Making New Vaccines Available in the Developing World", Proceedings of the Sabin Institute Annual Colloquium 2001.

[25] See e.g. "Patents in Genomics and Basic Research: Issues for Global Health", J. Barton, 2001, CMH Working Paper No. WG2: 13.

[26] For example the regional patents granted by the Organisation Africaine de la Propriété Intellectuelle (OAPI) in respect of Francophone Africa.

cost, and what the public wants, i.e. timely access to the patented invention. It used to be the case that each country could decide whether or not to grant patents for pharmaceutical products. If a company could not get a patent in a country, then manufacturers in that country were free to make a competing product and to some extent or other price competition could take place. **The TRIPS Agreement has totally changed this situation**. Patents for pharmaceutical products will have to be permitted by all WTO Members (except LDCs), at the latest by 1st January 2005. On the basis of paragraph 7 of the Doha Declaration, LDCs are able to put off granting patents for pharmaceutical products until 1st January 2016 (and neither need they enforce patents that have been granted till then). Generally speaking, the most important countries to seek patent protection in are core, rich markets and the locations of any competitors – this is why it is so significant in terms of pharmaceutical products that the middle income developing countries such as India, China and Brazil are subject to this TRIPS regime – if the source of any competing products can be 'choked off' then there is no need to seek patent protection for every potential market. India is perhaps the leading case of a country where this deadline is going to have a significant impact being home to some of the most significant generic producers, although Egypt is another important country in this category, other similar Members such as Brazil and China already having changed their law to permit the patenting of pharmaceutical products.

On top of the TRIPS Agreement however, a process of international patent harmonization intended to make it easier to obtain patent grant internationally (the Substantive Patent Law Treaty negotiations hosted by the World Intellectual Property Organisation (WIPO)) will likely only tilt the balance further in the favour of more widespread patent protection.

A high profile example of the phenomenon of such 'geographical' competition in the field of medicines has been that of certain anti-retroviral medicines. A number of Indian firms have produced generic versions of anti-retroviral medicines that have been patented in developed countries. These Indian firms have been able to do so because India was able to put off granting patents for pharmaceutical products until the 1st January 2005 under the transitional provisions of the TRIPS Agreement[27]. Given that the relevant anti-retroviral medicines have not been patented in India then Indian firms have been at liberty to produce their own versions. The Indian firms have exported their generic versions of these anti-retroviral medicines, notably to Sub-Saharan Africa, and price competition has therefore in effect taken place on the global market. The extraordinary price drop that this has brought about, of some 97%, has opened the door to be able to begin to treat the vast numbers of those HIV positive patients who now need treatment with antiretroviral medicines and indeed President Bush went out of his way to recognise this in his 2003 State of the Union address[28], although this perspective does not seem to have subsequently significantly informed the foreign trade policies of his administration. Conversely, from the perspective of the OECD patent holding pharmaceutical industry, this relatively transparent price competition can only be seen as extremely disadvantageous in terms of impacting profitability and therefore future performance.

[27] Although Art 70.8 TRIPS requires as a *quid pro quo* that a so-called 'mailbox' be set up to receive patent applications in the period between the TRIPS Agreement coming into force on 1st January 1995 and the date when the law changes to permit the grant of pharmaceutical product patents. The mailbox 'preserves' these patent applications so that, in the case of India, when the mailbox is opened on 1st January 2005 the patent applications may be examined and potentially granted under the new law.

[28] See e.g. http://www.usaid.gov/about/hivaids/excerpts.html for an extract of President Bush's address including, "AIDS can be prevented. Anti-retroviral drugs can extend life for many years. And the cost of those drugs has dropped from $12,000 a year to under $300 a year -- which places a tremendous possibility within our grasp. Ladies and gentlemen, seldom has history offered a greater opportunity to do so much for so many."

An example demonstrating elements both of 'scope' and 'geographical' competition, the Hepatitis B vaccine case, is discussed further below in this section.

Given the existence of the TRIPS Agreement and in particular the January 1st 2005 deadline, the possibilities for repeating these examples may be **severely limited** in the future.

(c) Under the provisions of the TRIPS Agreement, **patent monopolies are also limited in time** to 20 years from the filing date (so long as the patent holder keeps paying the necessary renewal fees). The TRIPS Agreement only sets a minimum however and a number of developed countries already provide extensions to this minimum patent term e.g. to compensate a pharmaceutical patent holder for the length of time that it took to obtain regulatory approval. Such provisions to extend patent lifetime are increasingly spreading to developing countries as well under TRIPS-plus bilateral or regional Free Trade Agreements, as noted above. The patent term extension may be simply an extension of the lifetime of the patent or an equivalent mechanism, such as the European Supplementary Protection Certificates.

Given the extraordinary value of some pharmaceutical product patent monopolies it is well understood that every extra year, month or even week is worth fighting for. In addition to processes directed to direct extension of the patent term, there is also a process known as 'evergreening', where successive patents are obtained for improvements or modifications of a product and, so long as the consumer or competitor is always moved to considering the 'latest version' of the product, patent protection for that product may in effect be prolonged beyond 20 years. An interesting example of this in the biotech patents field is the case of the "Boss" and "Cabilly" patents, involving an agreement between two companies to attempt to extend of the lifetime of patent protection relating to an important technique for the synthesis of antibody molecules[29]. Attempts such as these, properly or otherwise, to extend the lifetime of a very profitable patent or invention, used to be the domain of the private sector but it seems now that universities have become more involved in obtaining and exploiting intellectual property, they too are not immune from this type of behaviour[30]. Such extensions of effective patent protection will have a direct impact on the speed with which competition for a given patented product is likely to be introduced and therefore the speed with which the patent monopoly price begins to fall. As noted above in the introductory comments to the Access and IP section, the present lifespan of vaccine patents may already be too long for many in need and any extension of that lifespan will exacerbate that problem further.

There is a legal provision called the Bolar exception that allows activity relating to the registration of a generic product to be carried out during the lifetime of the patent thus the speeding up of generic competition, if not during the life of the patent then at least as soon as possible thereafter. In terms of application to vaccines, possessing the necessary vaccine production know-how will likely be a factor in being able to make timely use of such a Bolar exception.

[29] See e.g. "When Patents Persist", http://www.bio-itworld.com/archive/121503/insights_patents.html
[30] It is reported that Columbia University enlisted a Senator, an alumnus, to include provision for 15 month extensions for certain valuable patents of theirs in a few year 2000 bills; some 25% of its research budget apparently now comes from the licensing income it receives from its patent portfolio. See Scientific American, February 9th 2004.

The Hepatitis B vaccines

The case of the Hepatitis B vaccines is of interest to illustrate some of the issues outlined in the previous two sections[31]. The importance of studying this example cannot be understated[32]:

> "When the vaccine first became available over 20 years ago it cost $150 for three doses, 150 times more than the total cost of all six traditional EPI vaccines then in use. Its arrival on the market signalled an end to the "cheap vaccine era" and helped focus global attention on the increasing inequity in access to vaccines and immunization".

It has seemingly been used an example by both the CVI and WHO/WTO documents to show that patents do not represent a significant barrier to accessing new vaccines.

Plasma derived Hepatitis B vaccines

A first plasma derived vaccine, variously reported as building on work by the US National Institutes of Health in the 1960s and research conducted at the New York Blood Center under Dr Alfred Prince and Dr Barry Bloomberg in the 1970's, was first "brought to market" by Merck & Co, apparently in 1981. However the price at which this vaccine was brought to market in the United States and the complexity of the technology meant that there was little or no chance that this vaccine could be used in the developing world.

A different plasma derived Hepatitis B vaccine production technology was invented by Dr Alfred Prince of the New York Blood Center. It is reported that Dr Prince was specifically motivated to investigate and subsequently make his invention by what was seen as the shockingly high price of the Merck vaccine[33]. His invention was made with the express purpose of transferring the production technology to a vaccine manufacturer in the developing world, to enable an affordable Hepatitis B vaccine to be deployed where it was most needed. A South Korean vaccine manufacturer, Cheil Sugar Company, a subsidiary of the Samsung chaebol, eventually began production. Another South Korean manufacturer, Korean Green Cross Corp, also acquired similar technology as did others (by a variety of routes) and by the late 1980's there were more than ten producers on the international market[34]. There were seemingly no relevant patents anywhere to prevent the emergence of these competitors.

The Hepatitis B Task Force was set up in the '80s to address the lack of availability of a Hepatitis B vaccine in the developing world. Two founding members were Dr Prince and Professor Mahoney. When the Hepatitis B Task Force organised a sealed bid tender process in 1987 in Indonesia, where there were likewise no relevant patents, both Cheil and KGCC were able to bid with their vaccines. The stunning result was a drop in the prevailing global

[31] The history of the development and deployment of Hepatitis B vaccines is of particular interest to the issue of the impact of intellectual property on vaccines. It has already been widely cited (e.g. in the WHO/WTO and CVI documents), already treated as a case study (e.g. in "Immunization Financing in Developing Countries and the International Vaccine Market: TRENDS AND ISSUES", Asian Development Bank, 2001) and indeed made the subject of a whole book, "The War Against Hepatitis B", Muraskin, 1995.

[32] State of World's vaccines doc, p 43

[33] "Prince was incensed that the price was inflated far above what even an expensive technology demanded", p21, Muraskin *supra*.

[34] ADB report, p 43, *supra*.

market price of some $15-30 per dose offered by OECD vaccine firms to the $1 or less per dose offered by Cheil and KGCC[35]. Such a drop in price opens up whole new vistas for being able to provide the vaccine to those who most need it although this comes at the cost, presumably, from the perspective of e.g. an OECD vaccine manufacturer, of a massive drop in profitability.

Price history of plasma derived Hepatitis B vaccines

The reported graph of the price history of plasma derived Hepatitis B vaccines[36] begins at a high point of some $30 where Merck was the sole producer. A steep price fall follows, including in the mid to late '80s following the entrance of the South Korean competitors to the market, leading to a substantial turning point at a price of around $1 at the time of the Indonesian tender. The price continued to drop since then as more and more producers entered the market. The present price (1999) is quoted as around $0.50.

Recombinant DNA Hepatitis B vaccines

Recombinant DNA Hepatitis B vaccines arrived in very different circumstances. Biogen was granted a broad patent relating to rDNA Hepatitis B vaccines and voluntarily licensed Merck and SmithKlineBeecham to produce. The CVI document reports a reported maximum royalty rate of 15% (p 3), seemingly to demonstrate that patents do not significantly impact the price of new vaccines. However, the CVI document notes in the following sentence that "[T]he more significant increment in vaccine price comes not from the royalty costs but from the lack of competition during the patent period". In general a patent licensing situation cannot be expected to lead to the same fall in prices that market place competition will. There were countries in which a voluntary licence could not apparently be agreed and in Israel, a compulsory licence was granted in respect of the Biogen patent[37]. Towards what was the end of the natural lifetime of the patent anyway, the UK Biogen patent was revoked for being overly broad: it had tried to monopolize rDNA Hepatitis B vaccines made by any method but had only shown one rather narrow technique for doing so[38]. In general the patent situation was very different for the rDNA vaccines as there were relevant patents in place to protect at least the wealthy markets such as the US and Europe. Even if an emerging manufacturer were able to produce their own version of the rDNA vaccine, jumping the two hurdles that that TRIPS Agreement did not yet require their country to provide pharmaceutical product patents, and that they did have all the necessary know-how, they would not have been able compete in the wealthy markets till the expiry of the patents.

Price history of recombinant DNA Hepatitis B vaccines

The reported graph of the price history of the recombinant Hepatitis B vaccines[39] is not dissimilar to that of the plasma derived vaccines, beginning at a high point of some $40 where Merck was the sole producer. There is a steep price fall until a substantial turning point in the late '80s, early '90s at around a price of a few dollars. The rDNA vaccine price is not far above the price of the plasma derived vaccine into the '90s, through the expiry of the

[35] ADB report, p43, *supra*.
[36] ADB report, p 40, *supra*.
[37] See *infra* section 3.7.4.
[38] Biogen v. Medeva [1997] R.P.C. 1 H.L.
[39] ADB report, p 40, *supra*.
[40] ADB report, p47, *supra*.
[41] "A major factor that drove down the price of the recombinant DNA vaccine was competition with the plasma-derived vaccine", ADB report, p 45, *supra*.
[42] Mahoney, R, Pablos-Mendez, A, and Ramachandran, S. The Introduction of New Vaccines in Developing Countries III. the role of Intellectual Property. Vaccine, 2004, 22(5-6):787-793.
[43] MIHR Newsletter December 2003

Biogen patents in 1996 to a present (1999) price of around $0.60 per dose. It is reported that, whereas the plasma derived vaccine took six years to drop below $1 in price, it took twelve years for the rDNA vaccine to do so, although of course the different patent situation is not the only relevant factor[40].

Questions

The classic price history of a patented good where effective competition has been suppressed for the lifetime of the patent may be expected to look like a relatively stable high price until the expiry of the patent followed by a sharp fall as competitors are able to enter the market. This phenomenon is well known in the pharmaceutical industry. **The price history of the patented rDNA Hepatitis B vaccine,** used as an example by the CVI and WHO/WTO documents**, does not seem to follow the classic price history of a patent monopoly priced good.** Instead of a high price till the late 1990's when the Biogen patents expired or were revoked, followed by a substantial fall in price thereafter (which is what might have been expected), there was a continuous decline in price since launch, seemingly tracking the price history of the plasma derived Hepatitis B vaccine. This would not be too surprising if the **plasma derived vaccine were presenting steady and effective competition to the rDNA vaccine**, which it reportedly was[41] (and it is not yet clear but perhaps there may also have been other sources of competition by the late 1990's from emerging rDNA vaccine producers?). If this is so, then the case of the patented rDNA Hepatitis B would likely **not** be a particularly good example to show that patents *per se* are unlikely to present a significant barrier to access new IP protected vaccines. In fact, in this case there looks to have been a competing product which the patent(s) were not able to suppress which meant that the patent could not charge a true monopoly price. It cannot be assumed that for each potential vaccine patent monopoly there will be a highly skilled and non-profit motivated scientist or technologist directing his or her energies to inventing a competing vaccine that will be suitable for transfer, production and use in the developing world.

What would the rDNA Hepatitis B vaccine price history have looked like if Dr Prince had not been stimulated to invent his new plasma derived vaccine and transfer the technology to an emerging manufacturer? Assuming that the Korean plasma derived vaccines did indeed provide effective competition to the rDNA vaccine, presumably without that competition the price of the rDNA vaccine would have remained higher for longer? If the rDNA vaccine had not experienced any effective competition then presumably, the classic price history of a patented product might have been seen, only falling significantly after the patents had expired, or in this case, been revoked?

What lessons should be drawn from this in the post-TRIPS world, where patent protection of pharmaceutical products is becoming widespread? Professor Mahoney has been conducting research into the case of Hepatitis B vaccine development and production in Korea[42], and notes the following[43]:

> A possible additional effect of the TRIPS agreement is to prevent the kind of innovative work that the Korean companies did. Under TRIPS, patent holders will be able to obtain uniform and effective product patent coverage in all important markets. There will be no "Room to Operate." Thus an important question is the extent to which patent holders will seek to obtain and maintain global control even for markets they have little or no intention of pursuing.

3.3. Know-How and Competition

The importance of know-how to vaccines was touched on above in section 2.2. A crucial issue is whether or not the necessary vaccine production know-how is available to a given vaccine producer.

It seems that the difference at the present time between the technical capabilities of e.g. an OECD vaccine producer and an emerging vaccine producer in the developing world make the existence of such a know-how gap rather likely (at least in respect of the newer and more sophisticated vaccines). There is of course a great deal of variation in terms of emerging suppliers technological capabilities and some are quite sophisticated. Nevertheless, this is a crucial issue to investigate. Is there an important know-how gap between developed and developing country vaccine manufacturers? If there is, what is the extent of it? What can be done about it? What will the impact be in years to come?
In terms of comparing the effects of patents and know-how, it seems possible to say that the greater the technical gap between e.g. an OECD patent holder and a potential emerging competitor, the more likely it is that 'secret' know-how (and the body of more general technical know-how as well) will form the greater 'barrier to entry' for the competitor. By contrast, if the patent holder and the potential competitor are close in technical capabilities and equipped with much the same know-how, then it might be that the patent forms the more immediate 'barrier to entry'. This might perhaps be the case for example for a modified EPI-schedule vaccine, where many emerging manufacturers for these more simple products might have much the same level of know-how as OECD firms.

3.4. Undisclosed test or other data and Competition

The issue of the protection of undisclosed test or other data to vaccines was touched on above in section 2.3. In the light of the fact that each vaccine manufacturer apparently has to carry out their own clinical trials before their vaccine may be licensed (unlike the situation in medicines where bio-equivalence procedures may be used to avoid the necessity of repeating unnecessary clinical trials) this issue may have less impact on vaccines. However, to the extent that progress may be made for example on the issue of "well characterised products", this may permit greater equivalency or "comparability" to be established: in which case it might be imagined that this issue may rise in significance.

3.5 Other factors

It will be self-evident that there are many other factors involved in the dynamics of competition between different vaccines in the marketplace that have nothing whatsoever to do with patents. Consequently, even if a company is observed to have a *de facto* market monopoly, it cannot be concluded that patent rights are the sole or even the main cause. More careful analysis is required. It is possible that a monopoly situation has arisen not because of any patent rights but because of a know-how monopoly, as discussed above. Beyond intellectual property however, there are many other factors which could either incentivise or dis-incentivise vaccine manufacturers to enter a given marketplace. **Regulatory issues** are one obvious factor, increasingly high standards having made the process of licensure considerably more resource intensive that it used to be. Even if a vaccine has been developed and licensed however there are many factors that may impact the extent to which competition occurs, one such factor being able to operate with sufficient **economies of scale** for example. These further issues cannot be discussed further here.

3.6 Vaccine delivery devices

Given the different nature of vaccine delivery devices from vaccines per se, it can be expected that the respective market structures will be very different, as noted above in section 2.4. Intellectual property access problems to essential vaccine delivery devices may be more amenable to a solution if they relate to e.g. patents rather than know-how. It would be interesting to study the different intellectual property consequences that arise for vaccine delivery devices as a result of these differences.

3.7 Measures to increase access

A patent is a public policy 'tool' and can be used in a number of different ways. Contrary to a popular perception, in the first instance a patent is about gaining 'control' rather than just making profits. Exercising that control to make profits by excluding others from the marketplace is one way that a patent holder can choose to use their tool but it is not the only one (and even if they do exclude others, pricing decisions are still within the hands of the patent holder). There is nothing to stop a patent holder from choosing to make non-exclusive royalty free licences available to all or alternatively, and more simply, not enforcing the patent against anybody, in either case looking rather like there was no patent at all. Or a patent holder could choose another way, keeping certain countries as for-profit, just for the patent holder or for high paying licensees, but permitting others to operate under not-for-profit or low profit conditions. There is much that patent holders can choose to do to avoid patent related access problems. If not then there are at least in theory mechanisms available under TRIPS to attempt to enable price reducing competition without their consent. The following sections discuss tiered pricing, bulk purchasing (including procurement considerations) and voluntary and compulsory licensing respectively. Other measures such as e.g. "patent buyouts" are not discussed further here.

3.7.1 Tiered pricing

Tiered pricing is a classic mechanism by which vaccines have been made available to developing countries at lower prices than developed ones[44]. Pricing decisions are of course in the hands of the patent holder. A donation program, giving the necessary product away for free to those in need, may be regarded as an extreme example of a pricing decision. Where the same vaccines are used in the developed countries and the developing ones, a market containing both rich and poor parts exists, and the developing countries can perhaps take advantage of the R&D costs being largely carried by the developed countries.

'Parallel importation', which makes tiered pricing less likely over the area in which the parallel importation can take place, is seemingly virtually non-existent for vaccines due to the nature of the product and the way in which they are distributed. The WHO/WTO document indicates that (box 15, p97):

> Vaccines are a heat sensitive biological product. Since they are administered to healthy children, often by injection, the safety and quality requirements for vaccines are very high. Therefore their procurement and distribution are strictly controlled. In addition, essential vaccines are usually provided free of charge to consumers, greatly reducing their likelihood of leakage, resale and piracy.

These considerations make it far less likely that third parties will be able to buy up vaccine stock and exploit price differences between different markets through parallel importation. The administration of vaccines through public agencies at no cost to the patient may also reduce the likelihood of a situation where a patient in a rich country becomes angry when

[44] Note: the WHO and WTO Secretariats held a joint workshop in Høsbjør, Norway on 8-11 June 2001 to "examine the legal, institutional and political environment that would favor widespread use of differential pricing…", report and working papers available on WHO, WTO websites.

they find out that they have personally had to pay 10 or 100 times as much as someone in a poor country for that vaccine[45].

A significant challenge to the tiered pricing of vaccines must be so-called '**schedule divergence**', where different vaccine products end up being used in diverging vaccine markets. The Global Alliance for Vaccines and Immunization (GAVI) commissioned Mercer Management Consulting to report on procurement strategies and this report included an analysis of the global vaccine market structure which discussed the issue of schedule divergence[4647]:

> Increasingly, high-income country immunization schedules are diverging from those in low and middle countries. This trend threatens one of the bases for tiered pricing, whereby high-income and low-income countries bought the same products, but high-income countries' pricing covered most of the production costs. Historically, tiered pricing has been critical to affordability and broad access.

3.7.2. Bulk purchasing / procurement

The success of bulk purchasing is simply reflective of the fact that lower prices can usually be offered for greater volumes of product. Bulk purchasing processes do play a tremendously important role in the field of vaccines[48] as well as in e.g. the field of contraceptives. UNICEF, PAHO and the WHO account for a large fraction of global vaccine purchasing activities, in terms of volume if not dollar value. Bulk purchasing is inherently important for vaccines given the scale issues involved in vaccine production and the necessity to correlate production plans with effective disease burden estimation. The relationship between intellectual property and procurement is outlined further below in this section.

One form of high-volume purchase that may be particularly relevant for vaccines may be one that takes place ahead of time i.e. an advance purchase commitment. There are those that favour such a mechanism[49] although others are more sceptical[50]. There may likely be an issue that the efficiency of advance purchase commitments varies greatly in terms of how far down the product development pipeline the candidate product is. An advance purchase commitment may work better to stimulate a short dash from the later stages of development to the finished product than to stimulate long term research intensive projects. One example of the former is the trivalent (A, C, W135) meningitis vaccine that GSK agreed to develop and licence following WHO-led negotiations (pending the longer term development of a meningitis conjugate vaccine). As of mid-2003 it was agreed that 6 million doses would be made available for 1 euro per dose, a price considered affordable for African governments, the necessary funds having been raised after considerable advocacy efforts by MSF, WHO and other International Coordinating Group (ICG) members[51].

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[45] "One is struck by the extent to which good economic theory and good politics regarding differential prices do not necessarily mix" in "Differential pricing of Essential AIDS Drugs", P.J.Hammer, Journal of International Economic Law, December 2002, pp 883-912.

[46] See e.g. p 105, Mercer report, "Lessons Learned: New Strategies for Vaccines, Final Report to the GAVI Board", June 28, 2002, reproduced in Eight GAVI Board Meeting document, June 2002.

[47] Although the phenomenon had been raised before this e.g. see Milstien et al., "Divergence of vaccine product lines in industrialized and developing countries" Paper presented to the Strategic Advisory Group of Experts of the World Health Organization Department of Vaccines and Biologicals. 2001.

[48] See Asian Development Bank report, *supra* note 28, p 39 *et seq*

[49] Michael Kremer has provided influential analyses to both the CMH and UK government indicating the use of APCs as a particularly cost-effective intervention for the development of new health products. It is understood that the Gates Foundation is presently looking at vaccine APCs in particular.

[50] Note e.g. forthcoming analysis by Andrew Farlow, Oxford University.

[51] See e.g. http://www.accessmed-msf.org/campaign/men01.shtm

IP and Procurement

There is clearly a close link between bulk purchasing and intellectual property where procurement strategies are considered. **The remarkable reduction in the price of Hepatitis B vaccines obtained by the Hepatitis B Task Force discussed above in section 3.2 was achieved through the use of competitive tendering.** The point of a competitive tender process is of course that a number of parties have to compete against each other in a bidding process and that competition should ensure a lower price, or otherwise superior conditions etc. This does not sit well with the concept of IP however, where monopoly rights are provided to exclude competition.
In theory, one procurement option is 'respect for IP rights' and to refuse to accept bids from any supplier that have actual or potential IP problems. Many procurement policies will have something like a 'hold harmless' clause, which is to say that the entity doing the procurement will be indemnified by the supplier for e.g. any liability arising out of IP infringement claims relating to the supplied goods. Although this is fine in terms of removing liability from the entity doing the procurement, it does not go to the heart of the problem. If potential suppliers know that there is a patent on a given product and that there are e.g. many years of the patent life yet to run, they will likely not invest resource in developing their own version of the product. Even if they had their own version ready to be supplied, if it would infringe a valid patent, the patent owner could obtain e.g. an injunction to prevent that product from being supplied, as well as e.g. damages. This problem may be exacerbated if a patent right could be used to prevent a potential competitor from ever being able to be licensed (see above, section 2.5). This option is likely to have the support of IP owners but will not result in the advantages that a competitive tender is supposed to provide in that that there will be no other suppliers apart from the patent owner (or their licensee) from whom to procure. It is conceivable, although seemingly unlikely, that a patent owner would agree to licence a competitor either up-front or after that competitor won the bid. Presumably, a royalty payment would be involved.

In theory an alternative procurement option is 'respect for the IP system' and to utilise powers under the TRIPS Agreement, such as compulsory licensing, to permit any supplier capable of demonstrating e.g. the requisite quality standards to bid whether or not the IP owner consents. This option might therefore look rather more like the Hepatitis B tender. Even in a post-TRIPS world, if there were any other suppliers capable of bidding with competing products, this option would encourage competition, and would likely result in lower prices, or otherwise superior conditions, but it will clearly not have the support of IP owners (although they will still have to be compensated with an adequate royalty)[52]. Again, the issues of compulsory licensing and obtaining licensure would have to be resolved.

For an overview of issues relating to the procurement of HIV/AIDS medicines which deals concretely with the subject of the impact of intellectual property rights on procurement, it may be interesting to refer to the recent World Bank technical guide on that subject[53] – Chapter 2 and Annex 2 deal with the intellectual property issues.

[52] Note the UK 'Pfizer' case where the UK government used this option to supply generic versions of patented antibiotics to the National Health Service in the 1960's, Pfizer Corp v. Ministry of Health [1965] R.P.C. 261, H.L.
[53] "HIV/AIDS MEDICINES AND RELATED SUPPLIES: Contemporary Context and Procurement TECHNICAL GUIDE", World Bank, February 2004, available at: http://www.worldbank.org/.

3.7.3. Voluntary licensing

As noted above, a patent holder may utilise a patent to provide permission to other parties to carry out acts which would otherwise be patent infringements. This is a voluntary patent licence and usually comes at the cost of some royalty payments in return.

One mode of voluntary patent licensing would see a multinational patent holder (holding a portfolio of patents in many countries) offering a non-exclusive licence to any one else who wanted one. Another mode might see the multinational patent holder offering an exclusive licence to another company along with technology transfer, for example including all the relevant know-how, to help put this other company into the same position vis-à-vis manufacturing the product as the patent holder. Another mode, where the patent holder does not wish to share all the technology with the licensee would see the patent holder provide a patent licence and a limited amount of technology transfer so that the licensee could carry out, for example, only a defined stage of the production.

There is evidence for a trend for OECD companies to carry out high-technology bulk production themselves but to enter into agreements with emerging manufacturers in developing countries to finish the packing and filling stages of production as discussed below in the technology transfer section. Whether or not the patent holding OECD companies would see benefit to themselves in progressing beyond that arrangement to one where the developing country emerging manufacturers acquired the bulk production technology so that they could grow to become competitors of the OECD companies is not clear. This may well merit further investigation, see section 5 below.

One fundamental issue with voluntary licensing, as is recognised in the CVI document, is that the contribution that royalty payments make to pricing will very likely be less significant than the lack of competition. In a licence situation "tooth and nail" competition between third parties will be replaced by a managed relationship between licensor and licensee. **Voluntary patent licensing cannot therefore be expected to lead inexorably to lower prices in the same way that market competition does**. QUESTION: Is it less likely that the massive price reductions of the sort offered by Cipla for antiretroviral medicines in 2001 or by Cheil or Korean Green Cross for Hepatitis B vaccines in 1986 would have occured if Cipla had been GSK's licensee or KGCC Merck's licensee? If the answer is that it is not likely, then prices for these ARV products, or for the Hepatitis B vaccines would have remained higher for longer.

The contemporary issue of dense 'thickets' of patents all relating to a given target but with different patents owned by different entities claiming monopoly rights over different aspects of that target will be discussed below in the R&D section. It is possible for patent holders to provide each other with voluntary 'cross-licences' to solve such problems. Alternatively, for very complex situations, it is possible for all the patent holders to put their patents into a voluntary 'patent pool'[54], following which a single licence can then be given in respect of the whole pool. There are competition law issues involved in such cross licensing and patent pools but they can play a helpful and effective role. Given the increasing amount of potentially relevant intellectual property and the potential complexity of the licence arrangements, the notion of 'licence mapping' has been suggested (by analogy to 'patent mapping').

[54] See for example, "Institutions for Intellectual Property Transactions: The Case of Patent Pools", R.P.Merges, Chapter 6 in "Expanding the Boundaries of Intellectual Property", ed by Dreyfuss, Zimmerman & First, Oxford University Press, 2001.

There are also rather more complex and less 'traditional' models for IP licensing which have been receiving a great deal of attention in terms of their ability to bring together partners from the public and private sectors in what are called, not surprisingly, Public-Private-Partnerships (PPPs). These are discussed below.

3.7.4. Compulsory licensing

Compulsory licensing is potentially an extremely important tool in mitigating the effects of patent monopolies[55]. There can be times when public interest demands that the patent monopoly be 'broken'. The possibility of carrying out compulsory licensing and the freedom available to choose the grounds on which to do it was re-confirmed in the Doha Declaration. One example of a compulsory licence that has already been granted in the vaccine field was that resulting from an Israeli patent case relating to the Hepatitis B patent of Biogen[56], as noted above in section 3.2.

Also as noted above however in section 3.3, the difference in technical sophistication between e.g. an OECD originator vaccine firm and an emerging vaccine firm may be such that there is a substantial gap in know-how between the two. If the emerging supplier cannot develop this missing know-how by itself, or cannot contract with another firm to develop and transfer to it the necessary know-how[57], then a 'naked' compulsory patent licence may not be of much assistance: although the threat of the patent holder taking legal action to stop vaccine development and production would have been lifted this would have no practical consequence if the emerging supplier could not develop or make the vaccine in the first place. Again, the MVP model may be of some interest here, as discussed below in section 4.6.

Given that a compulsory licence permits certain activities without the consent of the patent holder, it is no surprise that the use of compulsory licensing is strongly opposed by the patent holding OECD firms and the OECD governments who represent them. There are considerable political issues that arise as a result. An emerging supplier with sophisticated technical skills perhaps might in theory be able to compete aggressively with an OECD firm by means of compulsory licensing. However, that emerging supplier might instead be wary of entering into antagonistic competition with the OECD firms. This is perhaps to some extent illustrated by the comments of the Korean Green Cross Corporation when they won the Indonesian Hepatitis B vaccine procurement tender as discussed above[58]:

> "As an interesting aside on the complexity of pharmaceutical competition, the KGCC begged the task force not to announce publicly what their winning bid was. They said they were afraid of the effect of such information on both their normal market and their business relations with other commercial companies. They did not want to anger their competitors. Of course the Task Force could not agree to such a request since the low price was a major weapon in its bid to have other companies follow suit."

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[55] See e.g."Intellectual Property Rights in the WTO and Developing Countries", Jayashree Watal, Kluwer Law International, 2001, p317 et seq, referred to in section 2 above; "Intellectual Property Rights and the Use of Compulsory Licences: Options for Developing Countries", South Centre TRADE Working paper No.5, Correa, October 1999; "Towards a New Fashion of Protecting Pharmaceutical Patents in Africa – Legal Approach", Tshimanga Kongolo, IIC, Vol.33, No.2, 2002; see e.g. the many resources on compulsory licensing at http://www.cptech.org..

[56] See "Compulsory Licence for the Manufacture of a Hepatitis B vaccine", Michael Cohn, Patent World, October 1997, pp 27-29

[57] And also perhaps bearing in mind the possibility of compelling the transfer of the know-how, see section 2.2 above.

[58] See Muraskin, p97, *supra* box 1.

It might also be possible, given the apparently close cooperation between governments and private sector suppliers that governments might be reluctant to antagonise patent holding OECD multinationals.

If the situation emerges that vaccine producing firms are not interested in applying for compulsory licences or that governments are not willing to grant them, then one of the most potentially effective tools for dealing with the potentially ill effects of patent monopolies will have been foregone and **single suppliers may become an increasingly common occurrence**.

The notion of a 'voluntary' patent pool has been mentioned above. There is also a corresponding 'compulsory' patent pool, a leading example of which was a patent pool formed by the US government in the First World War to enable the wartime manufacture of aircraft[59].

Compulsory licensing also has a strong link to the more general issues of competition law and antitrust, which may also have interesting application in the context of vaccines, in particular given the structure of the global vaccine market (few suppliers – few purchasers).

3.8. Conclusions on IP and Access

This section opened by contrasting two different views of the impact of IP on access to vaccines: one drew attention to the disastrous effects in terms of lives lost of having to wait some decade or so before getting access to an affordable version of a patented vaccine, whereas the other instead indicated that there didn't seem to be any particular problem. It is clear that by their very nature patents, and other intellectual property rights, are likely to raise prices of IP protected vaccine above where they would be if they were subject to competition. It does seem to be the case though that, so far, there haven't been any cases obviously in the public eye where e.g. an essential vaccine was being sold at $30 per dose by one vaccine manufacturer although another manufacturer was capable of supplying the same vaccine for 30¢ a dose, if only a patent wasn't preventing them. However, it is also true to say that the full effects of patents for vaccines have not yet been felt, as the relevant provision of the TRIPS Agreement is only entering into final force on 1st January 2005. TRIPS-plus provisions in new bilateral or regional trade agreements will affect matters further. A case often used to suggest that patents do not in general contribute significantly to high vaccine prices, that of Hepatitis B, does not seem on examination to be a wholly good one – it seems instead that there existed a competitor to the patented vaccine which was able to prevent the patent owner from pricing in a truly monopolistic fashion. Looking at the impact of IP on access to, in particular, medicines, the CIPR Commission (see section 3.1 above) found on this important issue that[60]:

> More generally, as the TRIPS Agreement is implemented, the supply of generic copies of new medicines will be prevented. At present the threat of international competition with generic suppliers of copies of patented drugs is a restraining factor on the prices that can be charged in countries with no patent regimes, and to a lesser extent in countries with patent regimes where there is a credible threat of compulsory licensing…Means will need to be found, within the patent system and outside it, to generate the competitive environment that will help offset the adverse price effect of patents on developing country consumers.

[59] See e.g. the presentation of James Love on the creation of an essential health care needs patent pool to the recent Barcelona XIV International AIDS conference, http://www.cptech.org/slides/jameslove-barcelona.ppt

[60] CIPR report p 38, see section 3.1 *supra*.

Whether the measures that have to a greater or lesser extent facilitated access to patented vaccines in the past will be able to do so in the future remains to be seen. Issues to examine further in terms of characterising IP related access problems and considering what may be done about them are outlined in the 'options and directions to consider' section below.

4. IP and R&D for vaccines

4.1 Vaccine R&D

There is a wealth of evidence to demonstrate that there is insufficient R&D being carried out into the health needs of poor countries. A widely discussed report of the Global Forum for Health Research[61] drew attention to what has become known as the 10/90 phenomenon, that only 10% of global R&D spending is directed at the health needs of 90% of humanity. The recent WHO/UNICEF/World Bank document, "State of the World's Vaccines and Immunization"[62] says the following about the state of global R&D for vaccines:

> "Despite major breakthroughs in the development of new vaccines over the past two decades, children in developing countries are disadvantaged by vaccine R&D agendas tailored to the needs of children in wealthier countries. The problem is three-fold: first the low uptake of new vaccines in developing countries; second, the neglect of "low-profit" vaccines for mainly developing country markets; and third, the differences in the prevalence of disease causing organisms in developing and developed countries"

These three problems are not independent, the comparative poverty of developing countries being a central feature. If a given disease-causing organism is only prevalent in a poor country then necessarily the market for the relevant vaccine will be low or zero profit and hence, very likely, commercial development of this vaccine will be neglected. Likewise, the low uptake of new vaccines in developing countries has a number of causes but the high prices of new vaccines compared to the purchasing power of the developing country will be a strong factor.

The public sector does carry out research into the health needs of developing countries which need not be commercially directed, as will be discussed below, but traditionally has not taken the fruits of such research through to a finished product. That has typically been left to the private sector. In turn, the private sector has carried out a certain amount of R&D into the health needs of developing countries. Comparatively recently new initiatives such as research labs and public private partnerships have been spurred[63]:

> For example, AstraZeneca opened up a Discovery Research Facility to undertake R&D into tuberculosis in Bangalore in India. A similar research center specialising in diseases of developing world was set up by GlaxoSmithKline at Tres Cantos in Spain. Novartis is currently launching a new R&D facility in Singapore where research of new drugs and vaccines for tuberculosis and dengue fever will be conducted;
>
> The pharmaceutical companies, working closely with different partners, have proven that they can both deliver viable solutions to health problems in emergency situations (such as meningitis) and provide for long-term sustainable programmes aiming to eradicate diseases endemic in developing countries. The latter is the case of many

[61] http://www.globalforumhealth.org
[62] See *supra* section 3.1.
[63] See "Neglected Diseases and the Pharmaceutical Industry", IFPMA, December 2003

diseases such as blinding trachoma, guinea worm, leprosy, lymphatic filariasis, polio, onchocerciasis (river blindness), or African trypanosomiasis (sleeping sickness).

However the lack of market incentive associated with the health needs of the developing world has prevented the large scale intervention of private sector firms. The amount of resource that has been invested in research and development directed at the health needs of the poor, by both the private and public sectors, has fallen and continues to fall far short of what is needed[64]. Given that the TRIPS Agreement is now a mainstay of the health innovation system, what contribution has it made?

4.2. IP incentivising vaccine R&D

The central mechanism for stimulating private sector R&D should of course now be the TRIPS Agreement, mandated for developed and developing WTO Members alike. Given that the TRIPS Agreement extends the intellectual property system to poor countries as well, presumably the lure of intellectual property rights in developing countries is supposed to incentivise the private sector to commit R&D resources to the needs of the poor, just as it has with the rich?

The CVI document frames the relationship between IP and R&D in the following terms (page 4) "the *assumption* is that innovation, and some financial risk taking, is thereby encouraged" and (page 11) "…IP systems in the long term have shown their ultimate value in fostering innovation and the large financial investments required to develop ideas into safe and efficacious vaccine products, which eventually benefit all children."

In fact, the basis on which this assumption is grounded, and the perceived developed country success of the IP system in fostering innovation in the longer term, has of course been the existence of a viable underlying market. So the central question must be, is it safe to assume that just because the intellectual property system has worked to deliver acceptable innovation in the context of a rich, developed country, that it will do so in the context of a poor, developing country? **In fact it is not possible to divorce the effectiveness of the IP system in stimulating R&D from the viability of the underlying market in which it provides monopoly rights**. Needless to say there is no relationship between the size of market in human terms and the size of the market in wealth terms – for the purposes of the functioning of IP it is only the latter that counts.

4.3 R&D and the underlying market

The 2001 report of the Commission on Macroeconomics and Health (CMH) adopts a model (p79) of three different types of diseases to discuss why R&D has taken place for some diseases and not others. Type I diseases are widely prevalent in both rich and poor countries. Examples of communicable diseases of this type are measles, hepatitis B and *Haemophilus influenzae* type B and examples of non-communicable diseases of this type are diabetes and cardiovascular diseases. R&D incentives are present in respect of this disease type so products do get developed and the main policy issue for developing countries is access to these often patented products. Type II diseases, 'neglected diseases', are present in both rich and poor countries but the bulk of the incidence of the disease is in the poor countries. HIV/AIDS is an example of this type of disease and although R&D incentives work to some extent such that substantial R&D is underway, it is by no means in proportion to the disease burden. The case of TB as another example of this type of disease is even more striking. Type

[64] In terms of vaccine needs, note e.g. Institute of Medicine reports on establishing priorities for vaccine development (1985a, 1985b, National Academy Press, Washington DC) summarized in "History and Commentary", Jordan, W., 2002, pp5-19 in "Accelerated Development of Vaccines 2002 The Jordan Report 20th Anniversary", NIAID, NIH, http://www.niaid.nih.gov/dmid/vaccines/jordan20/

III diseases, 'very neglected diseases', are those that are overwhelmingly or exclusively suffered in poor countries. R&D incentives do not work well for this category. The CMH report indicates that (p78) "the basic principle that R&D tends to decline relative to disease burden in moving from Type I to Type III diseases is a robust empirical finding".

The intellectual property rights provided for under the TRIPS Agreement are now supposed to be the primary "R&D incentives". It can be no surprise that the amount of R&D that IP is capable of stimulating varies directly with the wealth of the relevant market in the way that the CMH present.

On the issue of IP and the stimulation of R&D, the CIPR report (see section 3.1 above) similarly finds that[65]:

> So what role does IP protection play in stimulating R&D on diseases prevalent in developing countries? All the evidence we have examined suggests that it hardly plays any role at all, except for those diseases where there is a large market in the developed world (for example, diabetes or heart disease).

4.4 Private Sector view: incentives and disincentives for vaccine R&D

An overwhelmingly important driver for any private sector vaccine firm, in terms of committing R&D resources, must be the possibilities for a profitable return on their investment. The Mercer report[66] indicates that overall R&D in the vaccine industry for the year 2000 is up to $750 million. This is of course a good thing but, from the perspective of the developing world, R&D *simpliciter* is not good enough, it has to be the right sort of R&D, to meet the needs of the developing world.

Rich markets will always likely present attractive prospects for the private sector. Companies will naturally want to carry out R&D directed at this sort of market and then obtain patent rights to try to reap a reward. In a perfect situation the rich consumers can pay the premium for the patented invention and it can be made available to all who need or want it. For companies and consumers alike this would be a mutually beneficial outcome. In OECD markets the phenomenon of the $1 billion 'blockbuster' vaccine product is known, just as with blockbuster medicines, one example of the former perhaps being the pneumococcal 7-valent conjugate vaccine (Prevnar) marketed by Wyeth Vaccines.

As noted above, in terms of the CMH disease types, it can be no surprise that the intellectual property rights provided for under the TRIPS Agreement tend to stimulate more R&D for type I diseases than type II diseases, simply because there are more rich people suffering from diseases of type I than type II, and tend to stimulate little if any R&D for type III diseases, because they are only suffered by poor people.

There will very likely be differences in approach between OECD vaccine manufacturers and emerging vaccine manufacturers in the developing world in terms of acceptable profit margins. There may be situations where, due to a large and acceptably wealthy aggregate market in developing countries, a high sales volume even with a much lower (e.g. far from 'blockbuster') profit margin may be attractive to an emerging supplier even if not to an OECD firm, as the MVP project has noted[67](see section 4.6 below):

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[65] CIPR report p33, see *supra* section 3.1.

[66] See *supra* section 3.7.1. The report uses a vaccine market product model segmented into basic, enhanced and proprietary pediatrics, and adult/travel categories.

[67] See "Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries", Jódar, LaForce, Ceccarini, Aguado & Granoff, The Lancet, vol 361, May 31st, 2003.

> We had assumed that a profit margin of about $0.50 per dose for 25 million doses per year would be a sufficient return on investment, if the public sector were providing the investment. However, if the costs of development also included opportunity costs that might be estimated at $200–500 million for a vaccine company with a promising research pipeline, then the return on investment from sales of the meningococcal vaccine would be perceived as insufficient…Finally, MVP negotiated a contract with a large manufacturer in Asia (Serum Institute of India, Pune, India)…They are willing to sell 25 million doses per year of group A meningococcal lyophilised conjugate vaccine in tendose vials for less than $0.50 per dose, which includes cost of depreciation of facilities and an acceptable profit margin…. In short, what was viewed by established vaccine companies in Europe or the USA as an opportunity cost, was seen by the developing country manufacturer as an opportunity—[among other things]…the prospect of sales to Africa of many doses of vaccine at a low but profitable price for an estimated 10 years or more…

It is likely that entities such as WHO, UNICEF, PAHO and national governments will play an important role as buyers in such a market.

In respect of the "most or very neglected" diseases there may be little or no profit incentive at all for private sector firms, even for emerging vaccine suppliers willing to make much lower profit margins that OECD vaccine firms. No possibility of profit very likely means no private sector R&D. **The highest international intellectual property standards could be adopted in these countries, or even higher, and still it could not be expected that private sector R&D for these diseases would automatically be stimulated**.

The situation for any given disease(s) or rather vaccine product is likely to be dynamic rather than static, and there may be an evolution through different types of markets. The phenomenon of 'schedule divergence' noted above may likely have the effect of splitting what was previously a overall viable market into two different markets, a rich market with one set of needs and a poor market with another. Naturally, it can be expected that the profit seeking private sector entity will address their R&D resources to the rich market alone, an example of which might be the Measles / MMR vaccines.

There are other possibilities than just considering the 'natural' viability of the relevant market. There is the case of 'making a market' where none existed before through the provision of external funds. The GAVI / Vaccine Fund may be an example of such a mechanism, where the Gates Foundation provided an initial $750 million. The funding time periods and sustainability will likely be key issues in this case. There is the possibility of a private sector firm agreeing to carry out research into a neglected disease application due to the possibility that the science or technology developed will have a closely related application in a rich market. There is also the possibility that the private sector may engage in a certain amount of R&D even if it is not perceived likely to be per se profitable but if reputational or "public relations" advantage may be gained by it.

The discussion of Public-Private-Partnerships below will also return to some of these issues as, fundamentally, what the intellectual property agreement at the heart of the PPP will likely try to do is tie an unattractive or not viable market to an attractive or at least viable market, so that the private sector partner will be incentivised to carry out R&D serving the former in the hopes of the securing profits from the latter.

It is clear, as the converse of the above discussion of incentives, that the private sector will be dis-incentivised in profit terms from working on vaccine products for poor markets, especially for diseases of type III above. Although society may obtain tremendous benefits from a successfully deployed vaccine, it may be that the private sector vaccine manufacturer captures

only a small portion of the beneficial return. A rather bigger issue than the returns from poor markets is the possibility that the nature of vaccines compared to medicines is inherently disincentivising for the profit-driven private sector. Compared to the potential profits that can be foreseen from a medicine that might need to be taken frequently over a long period of time, a vaccine, perhaps given once or only a few times, is likely a far less attractive prospect. Other potential dis-incentives to work on vaccines include for example the scientific and technical complexity and liability issues relating to the sensitivity of vaccine production (e.g. the removal of the rotavirus vaccine from the market).

It can be no surprise that a range of supplementary measures, over and above the intellectual property rights provided under the TRIPS Agreement have been created to further incentivise the private sector to work on vaccines for the health needs of developing countries (and more widely non-viable markets) including measures to lower the cost of developing the vaccine, or further measures to reward having developed a successful vaccine ("push and pull" measures)[68]. Public-Private-Partnerships (PPPs) are also playing an important role in engaging the private sector as will be discussed below. It is absolutely clear however that the **need for these supplementary measures is, in effect *confirmation* of the fact that a patent system is not always sufficient to stimulate R&D for the developing world**.

QUESTION: If IP is not working as an incentive to stimulate R&D for the needs of the developing world, are extra incentives the way to solve the problem, or could a wholly new R&D system be considered? Are the incentives presently suggested efficient in cost/benefit terms?

4.5 Public sector vaccine research (and development?)

Public sector spending plays a very significant role in health related research. One source[69] estimates that of an estimated $70 billion on health related global R&D in 2001, some $30 billion was expected to come from public sources. A considerable fraction of this public money came through the US National Institutes of Health, some $18 billion. Another source[70] puts a public sector health spending figure of $37 billion in 1998, of which only $2.5 billion was spent in low and middle income developing countries[71]. Vaccine research and development in general has received a substantial boost from the entrance of the Bill and Melinda Gates Foundation into the field.

Historically, intellectual property and 'return on capital invested' considerations have been far more important for the private sector than the public sector. As noted above, the public sector might have been thought of as generating public goods, potentially 'Global Public Goods', whereas the private sector has often relied on capturing high returns from proprietary products (even if these were 'built upon' a public base). A particularly interesting recent example of a public sector project creating public goods of enormous value is the Human Genome Project[72].

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[68] See e.g. "Using Intellectual Property Regimes to Meet Global Health R&D Needs", Kettler, Journal of World Intellectual Property, pp 655-679.
[69] "The Role of Intellectual Property and Licensing in Promoting Research in International Health: Perspectives from a Public Sector Biomedical Research Agency", Keusch & Nugent (of the Fogarty International Center, NIH), Commission on Macroeconomics and Health Working Paper, WG2:7, p 5.
[70] UK Commission on Intellectual Property Rights (CIPR) report p 32
[71] Note also the EU 'framework' R&D programs.
[72] For the perspective of a figure centrally involved in not only the Human Genome Project but also the intellectual property issues, see "The Common Thread: Science, politics, ethics and the Human Genome", Sir John Sulston & Georgina Ferry, Corgi, 2003.

However, the world of public sector research has changed radically in the last few years. Against the backdrop of a perception that the US was falling behind its strategic trade competitors in innovation, for example the Japanese, questions were asked about why US universities were not succeeding in transferring the benefits of their publicly funded research to the private sector. As a result of the debate the Bayh-Dole Act was passed in the US[73]. The effect of the Bayh-Dole Act was to permit universities to take control of intellectual property generated as a result of publicly funded research. Universities were permitted to exploit their intellectual property through licensing arrangements with the private sector, as a spur to the efficient take up of publicly funded research in the private sector. One net result of the Bayh-Dole Act has been that intellectual property issues and concerns have moved 'upstream' into what was previously basic research territory. Concerns relating to this development have been expressed over what might be seen as the commodification of basic science through the increased focus on intellectual property ownership, a re-orientation of public research agendas toward areas that might prove profitable and therefore a subtle or not so subtle skewing of the role and behaviour of academia[74], in effect mirroring the behaviour of the intellectual property driven private sector. The example of Columbia University was given above, outlining the financial stakes now at play for some universities.

Even if the public sector could resist a re-orientation of its research agenda and could focus on public health need driven activity rather than profit-oriented activity, could it be imagined that the public sector could alone deliver, for example, a new vaccine product suited to the needs of the developing world?

One of the fundamental factors in vaccine development and production is that the public sector has not, or rather has seen no need, to develop the skills of the private sector in taking vaccine candidates through the long process of clinical trials and licensure to production and the market.

It has been seen as needlessly duplicative and inefficient for the public sector to develop such skills given that 'that is what the private sector is there for'. One of a number of problems that arise with this however is that, in opportunity cost terms, the development and regulatory approval of drugs and vaccines for the poor out of the public sector has to *compete* for that limited skill resource with the development and regulatory clearance of drugs and vaccines for the rich. In effect the **private sector being the only source of the skills needed for the last section of the developmental pipeline endows a powerful (private sector) monopoly in its own right**. Could the public sector not just buy in the necessary skills from the private sector, on a contractual "we pay you to do this work, rather than give you a monopoly in the end result" basis? GSK made the following comment on this point[75]:

> "Unless the private sector, which has the expertise in drug development, is expected to act as simply a contracted research organisation (which is most unlikely from a commercial perspective given the opportunity costs this would involve), it will need other guarantees of return for its efforts. Patent rights (or some other form of exclusivity) are likely to be required, again demonstrating the importance of patents as an incentive."

The skills monopoly over the last section of the developmental pipeline therefore puts the private sector in a strong position to demand exclusive rights over any products that are developed. Is this an efficient way of stimulating the necessary R&D? It is an expensive

[73] See Fogarty paper, *supra* note 60.
[74] See e.g. the Richard Horton review of "Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research" by Sheldon Krimsky in the New York Review of Books, March 11, 2003.
[75] See GSK comments on CIPR report.

matter to develop and licence a vaccine product, but how expensive exactly? How can it be known whether the monopoly rights granted wildly over-reward the private sector for their contribution, or whether they simply make a viable return on the resources they have invested? Typically, it cannot be known as these costs are treated as confidential but it is now an open question.

QUESTION: In terms of cost/benefit, how efficient is it to provide the private sector with an IP market monopoly in return for their contribution to vaccine development and licensure? How much reward is provided for how much input?

A distinction should be drawn of course between private sector entities such as the multinational pharmaceutical companies with 'in-house' skills, emerging manufacturers who may be developing or further developing these skills and for example, 'contract' clinical trial companies. It may be that if it is considered necessary, given the reluctance of the private sector to take forward candidates that are needed from a public health if not profit perspective, that the missing developmental pipeline skills could be bought in from organisations other than the multinational pharmaceutical firms or that a wholly new entity could be set up to meet the vaccine developmental pipeline and perhaps production needs of the public sector and/or PPPs. There has been for some time now been discussion of the possibility for the creation of a 'National Vaccine Authority, for example[76]:

> "The Council of the Institute of Medicine of the National Academies believes that the development of a National Vaccine Authority is long overdue…Moreover, the Council believes that establishment of a government-owned, contractor-operated facility for research, development, and production of vaccines is essential to meeting the country's public health needs, particularly those related to bioterrorism and protection of our armed forces. This facility also should play a role in development and production of other vaccines required for the public health that are not currently available in the open market."

This issue does have a direct relevance to IP. The present private sector model calls for intellectual property right monopolies as a prerequisite for deploying their development skills. If an alternative model were to be demonstrated to deliver vaccines in a similarly effective manner, then there would be an interesting perspective from which to study the cost/benefit efficiency of the private sector IP based model.

QUESTION: Could a new (public) entity be considered to provide vaccine developmental and production facilities to the public or PPP sector?

4.6. Public-Private-Partnerships

To the extent that the respective strengths of the public and private sectors are held to be different and yet complementary, the concept of a Public-Private-Partnership seems very attractive. The possibility of a mutually beneficial situation is presented if both the public sector and the private sector can be induced to cooperate in playing their respective roles to deliver an improved public good outcome that neither the public nor the private sector could have delivered alone. Whether PPPs represent a viable new model is still not clear although much hope is being placed in them. PPPs are not a brand new concept and one example from 20 years ago which happens to involve vaccines and the WHO but which raises a number of issues of still very contemporary relevance is as follows[77]:

[76] Statement from the IOM Council on Vaccine Development, November 5th, 2001
[77] "The New Politics of Science", David Dickson, 1988, University of Chicago Press, p 211.

> "Early in 1983, scientists from the West Coast biotechnology company Genentech agreed to cooperate with research workers from the New York University Medical School on efforts to develop a malaria vaccine, potentially one of the most significant contributions of biotechnology to Third World health problems. Genentech promised to clone cells producing the antigen needed for the vaccine; in return, however, the company demanded exclusive rights to market the resulting vaccine. The New York University researchers refused, pointing out that their work was partly supported by the World Health Organisation, which expected in return access to any new products resulting from the research. And WHO was not prepared to grant any one company the rights to the vaccine – particularly in the light of growing demands from Third World countries that they be given the resources to establish their own vaccine production facilities. Genentech, not without a certain public rancor, withdrew from the project"

The Program for Appropriate Technology in Health (PATH) is another, more successful example of a long standing PPP[78].

There are now a number of vaccine related PPPs including e.g. those addressing AIDS (International AIDS Vaccine Initiative (IAVI[79])), TB (Aeras Global TB Vaccine Foundation[80]), Malaria (Malaria Vaccine Initiative (MVI)[81]), and e.g. Meningitis (Meningitis Vaccine Project (MVP)[82]).

The PPP concept can perhaps be viewed as still being in an investigatory phase, a comparatively recent article outlining the present state of affairs in the PPP world being "Public-Private partnerships for health require thoughtful evaluation" by Roy Widdus of the Initiative on Public Private Partnerships for Health (IPPPH)[83]. Widdus stresses the need in the article to recognise the fact that different PPPs have very different ways of working and it is not the case that there is just one model for a PPP. It is expected that the "current crop of PPPs can in time yield a body of evidence on which to construct evidence based "best practices"". A new organisation, the Centre for the Management of Intellectual Property in Health Research and Development (MIHR), has recently been set up and is expected to release 'best practice' IP management guidelines shortly.

The IP policy is likely the core of the PPP design as, as noted above, it holds out the hope of being able to tie a non-viable market to a viable market in such a way as to get R&D undertaken that would not previously have happened. By way of example the rights to a market could be linked geographically and/or by disease type. Some basic IP principles for PPPs have been outlined in the following terms[84]:

> IP is a key weapon for pharmaceutical companies in their pursuit of products and ultimately profits. PPPs must be as aggressive in the way they use IP as any commercial unit but for a different purpose – namely to pursue their social objective of getting quality, affordable products to developing country patients. This involves the negotiation of creative IP arrangements that do not scare off companies but also

[78] See e.g. PATH's principles for collaboration with the private sector at http://www.path.org/files/PublicSectorCollab-GP.pdf
[79] http://www.iavi.org
[80] http://aeras.org/
[81] www.malariavaccine.org
[82] www.meningvax.org/
[83] Bulletin of the World Health Organisation, 81 (4), 2003, Widdus.
[84] "Public Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty", Kettler and Towse (2002), p67

allow the PPP enough control to ensure their ultimate objective, a difficult challenge. The basic strategy has to be:

- Keep what you find…;
- Trade over any developed market for control of sales in developing country markets…;
- Establish explicit volume deals with the company partner so that if the company does not want to manufacture the product at volumes needed to meet the developing country need, the PPP can get the rights to the process and use contract manufacturing organisations to meet the supply needs;
- Trade any other disease use for control of the IP of the neglected disease…;
- If the partner chooses not to use the IP in pursuit of the designated product, the PPP has the right to take it back. The PPP therefore has the right not to be held up…;
- Explicitly address the issue of royalty rates for products sold in the paying markets…;
- Clearly determine the IP rights and conditions up front…;
- When in-licensing products or technologies, seek to control rights to outsource the project to third parties.

…the conditions PPPs place on IP negotiations – price guarantees[85], volume guarantees, market specifications – are new and risky. In IAVI's case, the IP agreements are also used as a mechanism to avoid delay in the introduction of vaccines to developing countries (in previous cases more than 10 years) by insisting that any vaccine will be made simultaneously available in developed and developing countries."

Although attractive in theory, whether the "new and risky" IP strategies of the PPPs will succeed remains to be seen. As suggested above, there will no doubt be a great deal of variation depending on the particular disease/vaccine circumstances that the PPP has addressed itself to.

IAVI is mentioned in the outline above and is interesting in that it appears to be the first of the new generation of PPPs to have its IP policy subjected to independent review[86]. In general the review found that IAVI is progressing well in terms of its core objectives. However the report cautions the need to reflect upon aspects of IAVI's policies, given the changed world of HIV/AIDS since 1996. On intellectual property the report says the following:

"Mechanisms to interact with the private sector that respect intellectual property rights and enable an appropriate return on investment are critical to successful interaction and engagement with this sector. Although IAVI has developed some important collaborations with the private sector, these interactions, especially with the pharmaceutical industry, remain an ongoing challenge for IAVI…One of the central points of IAVI's strategy is to use intellectual property rights as a lever to assure access to an eventual vaccine. This is clearly an admirable goal. However, the main difficulty we see with this approach is that it is unlikely that IAVI will ever be able to control, and thereby licence, all of the elements of intellectual property that will be needed to effectively develop an AIDS vaccine. There will always be a need to incorporate one or another element in the process that is likely to be controlled by other parties, such as a platform, a delivery vehicle or an adjuvant. It is important,

[85] Pricing clauses are strongly opposed by industry. Note discussion of removal of NIH pricing clause in Sabin report, p 18-20, *supra* note 21.
[86] "Independent Evaluation of the International AIDS Vaccine Initiative", April 2003

> therefore that *IAVI reconsider the balance it strikes between using its approach to intellectual property as the primary means to assure access and its aim of being certain that the most promising vaccine candidates continue to advance down the research and development pipeline*. This is not a simple task and IAVI remains actively involved in searching for a number of mechanisms to enhance access to an eventual vaccine." (italics added)

QUESTION: What caused the recommendation for a change in IAVI's IP policy?

In fact there has been a suggestion that even with the progress IAVI has made, that the efforts made so far to develop HIV/AIDS vaccines is wholly insufficient and that a substantially larger scale effort is needed[87], the Human Genome Project being mentioned as a model. One of the interesting challenges to be resolved with such an HIV/AIDS vaccine enterprise would be how to engage the private sector, as protection of their intellectual property rights and their commercial confidentiality would seem to be antithetical to the scientific culture of openness that the proposal calls for:

> The purpose of this approach is to create a systematic and coordinated pipeline of vaccine constructs that can be tested, evaluated, and redesigned. It is especially important that combination vaccine regimens are developed and tested early and that there is a systematic evaluation of the strains and antigens used. Ways must be found to address how proprietary issues, such as exclusive licensing deals, can be reconciled with open communication and vaccine development paths that combine materials and technology platforms owned by different entities. Creative solutions to this problem will be required if the critically important role of industry in this enterprise is to be realized.

QUESTION: Is an HIV/AIDS Vaccine Enterprise modelled on e.g. the Human Genome Project now needed and if so, how will the intellectual property tension between openness and proprietary information be resolved?

Another very interesting PPP proposal in terms of IP is that of the Meningitis Vaccine Project (MVP), involving two partners, the WHO and PATH, where a specific 'know-how' gap of the type discussed above may be sought to be filled through agreement with a contract research organisation for transfer to an emerging supplier[88]. Following a lack of interest from OECD manufacturers in their project, MVP explored the following option[89]:

> "We identified four critical components for production of the vaccine: (1) contract manufacture of group A polysaccharide and tetanus toxoid as intermediate components; (2) development of a commercially feasible conjugation chemistry process by experienced scientists; (3) transfer of conjugation process to a vaccine manufacturer in a developing country; and (4) scale-up of production, filling, and freeze drying of antigen, and packaging, storage, and distribution of finished vaccine by this developing country manufacturer."

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[87] "The Need for a Global HIV Vaccine Enterprise", Richard D. Klausner, Anthony S. Fauci, Lawrence Corey, Gary J. Nabel, Helene Gayle, Seth Berkley, Barton F. Haynes, David Baltimore, Chris Collins, R. Gordon Douglas, Jose Esparza, Donald P. Francis, N. K. Ganguly, Julie Louise Gerberding, Margaret I. Johnston, Michel D. Kazatchkine, Andrew J. McMichael, Malegapuru W. Makgoba, Giuseppe Pantaleo, Peter Piot, Yiming Shao, Edmund Tramont, Harold Varmus, Judith N.Wasserheit, SCIENCE, Vol. 300, 27th June 2003.

[88] See "Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries", Jódar, LaForce, Ceccarini, Aguado & Granoff, The Lancet, vol 361, May 31st, 2003.

[89] *ibid*

Suitable European partners were identified for a contract manufacturing stage (of clinical grade group A polysaccharide) and a design, scale up and technology transfer stage (for the development of a suitable conjugation process). A suitable emerging manufacturer partner was also identified, to whom the technology would be transferred, to carry out the final conjugation and filling, lyophilisation and packaging stages.

The IP arrangements that have been deployed to underpin this model do not seem to have been made public and it is not clear what the present status of this model is. It is interesting to note that one of the key attractive features for an emerging manufacturer about this model is that it involves the acquisition of technology and that technology may be used to develop other products for perhaps more profitable markets. The technology is envisaged to be acquired on a contractual basis, to fill that particular gap in the developmental pipeline. It is perhaps true to say that this may not be seen as such an attractive prospect by the OECD firms. It will therefore be interesting to observe the outcome of this project and irrespective of whether the alternative model is used here, or whether the OECD firms change their mind, or some other solution is found, the lessons learned will certainly be valuable for application in any subsequent attempt to use such an alternative model.

QUESTION: What is the present state of the MVP model?

4.7. IP dis-incentivising or hampering vaccine R&D?

In a notable paper entitled, "Can Patents Deter Innovation? The Anticommons in Biomedical Research"[90], Heller and Eisenberg discussed the following:

> "The "tragedy of the commons" metaphor helps explain why people overuse shared resources. However, the recent proliferation of intellectual property rights in biomedical research suggests a different tragedy, an "anticommons" in which people underuse scarce resources because too many owners can block each other. Privatization of biomedical research must be more carefully deployed to sustain both upstream research and downstream product development. Otherwise, more intellectual property rights may lead paradoxically to fewer useful products for improving human health."

This phenomenon of the "anticommons" underlines the possibility that in certain circumstances patents could have a disincentive effect on R&D. Given the technical sophistication of the field there are many different aspects of a vaccine product that may be patented. As patent rights have been granted to inventions further and further 'upstream', there is for example the **possibility that basic inputs or for example research tools used in the R&D process to lead to a new vaccine are also patented**.

This creates the possibility of a dense 'thicket' of patents, portions of which are owned by different entities, needing to be navigated through before a product can actually be produced. Just as the lure of a monopoly right may encourage the performance of R&D, such a 'thicket' of patents may be so difficult to navigate that companies may decide not to try to enter R&D for that product but move on to another target with 'less baggage'. In this sense it should be clear that it is a fallacy for even the private sector to presume that because they perceive IP to be good, that more IP is therefore necessarily better. This phenomenon is not merely an inconvenience for the private sector however.

A good example of the problems that this can throw up is the patent mapping undertaken by the Malaria Vaccine Initiative (MVI) to look at the patent status of the MSP-1 antigen[91].

[90] SCIENCE, Vol. 280, 1 May 1998.

There were potentially *thirty-nine* different families of patents found whose scope of monopoly was relevant to the MVI mission. Rather than moving on to investigate different targets, not so encumbered by patents, the MVI project had little choice but to try to press ahead[92].

Even where fewer IP rights are involved, patents on the necessary inputs and techniques for vaccine development may cause problems. The recently experienced Avian flu (H5N1) outbreak provides one contemporary example[93]:

> Standard production methods do not work for H5N1 vaccines, partly because the virus kills the chick embryos normally used to grow flu vaccine. Instead, the labs used a technique called "reverse engineering", which involves using genetic sequences called plasmids. The reverse engineering patent, however, is held by the biotech company Medimmune of Gaithersburg, Maryland, and the plasmids used are patented by various companies, all of whom will be entitled to payment if their property is used to make a commercial product…."If people felt we were facing a pandemic situation, we would waive intellectual property rights," says Jamie Lacey of Medimmune, but it is not clear whether the other patent holders would do the same. Of course, if a serious pandemic took hold, worries about patents would be swept aside[94]. But delays in vaccine production caused by the initial uncertainty could cost many lives. Wood[95] says there should be a clearly defined "trigger" point at which health authorities will be allowed to press ahead with plans for producing a vaccine without fear of violating patent laws.

QUESTION: What is the present status of the H5N1 vaccine in the light of the patent issues?

The issue of IP blocking access to either products or processes deemed necessary for vaccine development, rather than blocking access to a finished vaccine product as discussed above, must also be treated as a very serious problem. Lack of ability of develop the necessary vaccine is, in effect, just as much an access problem as trying to get access to a vaccine that has already been developed but e.g. is priced unaffordably. The public health needs of the developing world are so great that the vaccine candidates which are the most promising from a medical point of view must presumably be able to be taken forward and developed using the most effective tools.

QUESTION: How can access to patented 'upstream' vaccine research inputs best be managed?

There are some ways to address the problem, as noted above. The respective patent owners could perhaps agree to cross-licence each other, or form a 'patent pool'. For a case where a single fundamental patent is blocking the use of a subsequently obtained patent, the owner of that subsequent patent may apply for a particular 'dependent patent' form of compulsory

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[91] See e.g. http://www.malariavaccine.org
[92] CIPR report p127.
[93] New Scientist 21st January 2004
[94] No doubt many in the developing world will be rueful when they read this as, even following the Doha Declaration on TRIPS and Public Health, there continue to be very real patent issues associated with the use of generic antiretroviral medicines to treat HIV/AIDS patients there. It is assumed that what is meant by this statement is that if there were a serious pandemic that threatened one or more OECD countries, that patent concerns would be speedily removed, as happened with the anthrax scares in the US and Canada in 2001.
[95] N.b. there is no earlier mention of "Wood" in the article, it is unclear who he/she is.

licence[96]. For a more complex patent stack it is possible for a government to cut the 'Gordian knot' and force a patent pool through compulsory licensing of all the necessary patents.

The NIH has investigated the issue of the IP protection of research tools: "The growing difficulties encountered by scientists in gaining access to proprietary research tools reflect cautious and perhaps short-sighted responses of institutions and individuals involved in biomedical research to complex and shifting currents. These underlying currents, which include evolutionary shifts in the patent law, the Bayh-Dole Act, the missions of universities, the strategies of private firms, and the relationship between public and private research funding, are not directly controlled by NIH". The NIH provided a number of recommendations as a result of the investigation[97], including that "NIH should promote free dissemination of research tools without legal agreements whenever possible, especially when the prospect of commercial gain is remote" and that "NIH should develop and disseminate guidelines for recipients of NIH funds as to what terms are reasonable in licenses and MTAs, addressing both importing of research tools owned by other institutions and exporting of research tools created with NIH funds".

A recent January 2004 Ministerial level meeting of the OECD also addressed the issue of the impact of IP on upstream research[98].

> Although not widespread, cases of restricted access to patented inventions and delays in conducting or publishing research, indicate that governments must remain vigilant in ensuring that patenting does not unnecessarily hinder access to knowledge, reduce incentives to disseminate knowledge, or impede follow-on innovation. Ministers recognised the growing importance of patent licences and other market-based transactions in fostering knowledge diffusion and agreed that policy should encourage their development. Ministers further shared the view that IPR regimes need to protect researchers' access to fundamental inventions, such as through exemptions for research use of patented inventions

4.7 Conclusions on IP and R&D

As indicated above, there is a strong link between how R&D is carried out and the consequences for access and technology transfer than can be expected from it. Private sector R&D stimulated by the incentives offered by IP cannot to any great extent be expected to serve the (exclusive) health needs of poor markets, as for example the CIPR Commission found. Following Bayh-Dole, there are concerns about IP considerations moving upstream into basic research. The public sector lacks the development skills of the private sector – the traditional division of responsibility being research for the public sector and development for the private. It is conceivable that this could change in the future under certain circumstances. If IP-led R&D does not deliver for the health needs of the developing world and as yet the public sector cannot either, then other R&D possibilities may be considered, including public-private partnerships. Too many or too strong IP rights run the risk of strangling or otherwise hampering R&D. Issues to examine further in terms of IP and R&D are outlined in the 'options and directions to consider' section below.

5. IP, technology transfer and local production of vaccines

5.1. Technology transfer and the TRIPS Agreement

[96] Art 31(l) TRIPS

[97] Report of the National Institutes of Health (NIH) Working Group on Research Tools Presented to the Advisory Committee to the Director June 4, 1998, see http://www.nih.gov/news/researchtools/

[98] Science, Technology and Innovation for the 21st Century. Meeting of the OECD Committee for Scientific and Technological Policy at Ministerial Level, 29-30 January 2004 - Final Communique

For most of human history, technology transfer has taken place without any intellectual property framework. However, from the perspective of the early twenty first century and its pressing global needs, this typically haphazard historical process is not going to be equal to the task. Today 'technology transfer' can be understood as being a highly directed process although, as with PPPs, no single process definition can hope to capture its every form[99]. Technology transfer in the private sector may likely take place through the framework of the intellectual property system, in terms of patent licences and know-how agreements. However, technology transfer can also take place outside the intellectual property system framework, for example, in the public sector.

As far as the vaccine sector is concerned, as has been noted above, it seems that much of the knowledge that is needed to be able to produce 'new' vaccines is proprietary and is held only by OECD multinational companies. It is not true to say that these sorts of companies will never transfer technology to any country that does not have an OECD equivalent intellectual property enforcement system in place, the transfer of technology to China being an example[100], although the perceived market pull of China is often seen as a special case. For today's vaccine companies, it seems fair to think that they are far more likely to consider 'technology transfer' substantially in terms of an intellectual property system framework. The TRIPS Agreement is now the backbone of the global intellectual property system and it has several provisions that deal directly with technology transfer[101]. Article 7 provides that:

> "The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the *transfer and dissemination of technology*, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations" (italics added)

The preamble to the TRIPS Agreement also contains some relevant text, as does Article 8 and Article 40. However, it is Article 66.2 that has perhaps generated the most interest:

> "Developed country Members shall provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to least-developed country Members in order to enable them to create a sound and viable technological base".

It should be noted though that this provision only applies to LDCs. The provision will not ensure technology transfer, it can only been designed to encourage it: if a developed country Member introduces a tax relief provision to encourage technology transfer, then the developed country Member may likely have done enough to meet the obligation to LDCs under this provision, *even if no company ever uses it*.

A WTO Working Group was set up by the 2001 Ministerial Conference to look at the relationship between trade and technology transfer and the WTO Secretariat has now prepared some reports for Members in connection with the work of this group[102].

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[99] For an introduction in the pharmaceutical products field see e.g. "Access to Medicines: Transfer of Technology and Capacity Building", Assad Omer, Wisconsin International Law Journal, Volume 20, Number 3, Summer 2002. Note also the UNCTAD definitions.
[100] For a recent example see *supra* note 10.
[101] See e.g. "TRIPS – Development and Transfer of Technology", S.K.Verma, IIC, Vol 27, No.3, 1996.
[102] See e.g. "Revisiting the Technology Transfer Debate: Lessons for the New WTO Working Group", Roffe & Tesfachew, Bridges Comment, ICTSD (http://www.ictsd.org) and http://www.wto.org.

Whether or not technology is transferred through the IP system, for example under a patent licence, the patent system can and does play a role in helping the global diffusion of technological knowledge through the free availability of published patent specifications. However, although a patent specification has to explain at least one way of carrying out the invention, it will very likely not be easy to go from reading a patent specification to putting a complex invention into commercial production.

5.2. Technology transfer and the private sector: business models

Some of the key supplemental issues that have to be addressed before technology transfer is likely to take place though an intellectual property framework are raised in very specific and revealing terms by the CVI document (page 9):

> "In order to encourage market entry via technology transfer the potential licensee must convince IP holders that:
>
> 1. There is a viable and untapped or underutilized market for a vaccine.
> 2. There is a local producer able to attain and maintain GMP.
> 3. There is a local producer than can produce the product for the market more cost effectively than it could be produced externally (e.g. in the licensors home country).
> 4. The local producer will market its lower-production-cost product *only* within the designated markets; and
> 5. The local producer operates in a country which respects IP. In order for a licensor to enter a technology transfer agreement, that licensor must be convinced that such technology transfer not only present limited risk but also financial benefit."

IP is explicitly *not* a sufficient condition for technology transfer to occur. Condition 1 above draws attention for the necessity of having an underlying market. Condition 2 deals with manufacturing quality and the need to maintain GMP. Condition 3 calls for the local partner to demonstrate a cost advantage over other manufacturing sites. Condition 4 calls for the controlled segmentation of the market, so that the local producer cannot for example, use a cost advantage to compete with the patent holder in other markets, outside the authorised segment. Condition 5 calls for 'respect' of IP. The patent holder will want to be assured that they have and maintain effective control over the activities of the licensee, through the technology transfer agreement.

With reference to the introduction to this section, it should be noted that the conditions that the CVI document outlines are not in themselves critical elements for technology transfer in a general sense to take place. They are instead dictated by business model requirements for this class of technology transfer that is mediated through an IP framework. However, given the particular features of the vaccine market and the fact that it is seemingly only the private sector in the OECD that holds the necessary technical capabilities to produce the new vaccines, this mode of transfer will likely be especially important.

5.3. Other modes of technology transfer?

The CVI document concentrates on private sector modes of technology transfer where the IP owner effectively retains control of the technology. This is not to say that other modes don't exist however. One example is the seemingly not-for-profit transfer of Hepatitis B vaccine technology by Dr Prince to Cheil of Korea discussed above, described in 'lessons learned' terms as follows[103]:

[103] Asian Development Bank p47, *supra* box 1.

> Simple and inexpensive production processes for effective vaccines must be developed. For example, the Prince plasma-derived vaccine using flash heat technology is as effective as the vaccines developed using chemical processes, but much easier and cheaper to produce.
> Technology transfer to producers outside Europe and the US is critical to increasing competition and thus access to vaccines by developing countries.

Another example is the technology transfer envisaged by the MVP PPP, also as discussed above in section 4.6, which is envisaged to be carried out on a one-shot contractual basis. By analogy with the field of medicines, there is also the possibility of public sector technology transfer in terms of e.g. the Brazilian or Thai governments seeming willing to transfer their production technology for anti-retroviral medicines to other governments in the developing world. At least one major difference with medicines seems to be though that there don't seem to be any public sector entities in the developing world which have yet mastered all the necessary technologies at the same level as the OECD private sector firms, although for example the case of the Cuban Center for Genetic Engineering and Biotechnology (CIGB)[104] and its Meningitis B vaccine is perhaps an interesting counter-example.

QUESTION: How could vaccine production technologies best be transferred to the developing world?

5.4. Local production of vaccines

Even if the OECD multinationals other private sector entities could transfer the necessary production technology to developing countries or following on from the above section, if developing country governments who had developed production technology were willing to transfer it to other developing country governments or other entities, would it be sensible to do so? How is production most sensibly carried out, bearing in mind the strong scale effects observed in vaccine production? What is the distribution of vaccine manufacturing plants likely to look like?

There have been strong differences of opinion on the desirability of local production of vaccines. By way of one example, two members of the Hepatitis B Task Force, Dr Prince and Dr Mahoney, apparently had what became strongly different views insofar as Dr Prince reportedly believed that local production was essential for Africans and Asians to acquire the technical skills to take control over the medical products they utilised whereas reportedly Dr Mahoney had begun to doubt the quality standards attainable with local production (unless embarked on with a strategic decade(s) long process to raise regulatory standards) and favoured instead competition between high quality OECD suppliers[105].

A recent paper by Kaplan et al[106] comes to some fairly clear conclusions for the medicines field, although with a strong caveat that at the moment the datasets available are limited both qualitatively and quantitatively, of which but two are (p 51):

> In many parts of the world, there is no reason to produce medicines domestically since it makes little economic sense; and

[104] http://www.cigb.edu.cu (in Spanish)
[105] Muraskin, p21, p176, see *supra* box 1.
[106] "Is Local Production of Pharmaceuticals a Way to Improve Pharmaceutical Access in Developing and Transitional Countries? Setting a Research Agenda", Kaplan, Laing, Waning, Levison & Foster, Boston University School of Health, available at: www1.worldbank.org/hnp/hsd/documents/LOCALPRODUCTION.pdf

If local production is adopted by many countries, it may lead to less access to medicines, since there are no economies of scale in having a production facility in each country.

As regards the field of vaccines rather than pharmaceuticals, the scale issues may be even more important. If the question is posed as to what the likely distribution of production plants for 'new' vaccines might look like for the whole of Africa for example, it seems that considering one in South Africa and maybe one in Egypt is not going to be far from the truth[107].

QUESTION: Is widespread transfer of vaccine production technology to the developing world desirable, what are the pros and cons?

5.5. Vaccine technology transfer: other factors?

There are many factors outside intellectual property that may impact technology transfer for e.g. vaccine development or production. By way of one example, it seems conceivable that the present global sensitivities associated with R&D or any capabilities in the field of bioterrorism could have an impact on technology transfer in the vaccine field, whether in offensive (e.g. bioweapons) or defensive (e.g. as part of an anti-bioterrorism global pathogen surveillance program) terms.

5.6 Conclusions on IP and technology transfer

As indicated above, there is a strong link between how R&D is carried out and the consequences for access and technology transfer than can be expected from it. The TRIPS Agreement has provisions to encourage technology transfer but it cannot guarantee it. Private sector technology transfer may be more likely with an appropriate IP framework in place but there are many other business case conditions that have nothing to do with IP that need to be satisfied as well before it will. There is perhaps little incentive for e.g. OECD vaccine producers to transfer 'core' production technology to emerging producers in terms of the tension between strategic cooperation and strategic competition. There may be some other interesting models to consider including within the public sector and through public-private partnerships utilising contract research and development and transfer of the technology developed. The issue of 'local production' is an important one in terms of judging how much technology transfer, and to whom, may best serve public health needs. . Issues to examine further in terms of IP and technology transfer are outlined in the 'options and directions to consider' section below.

6. Options and Directions to Consider

A variety of suggested issues for further study are raised, to guide discussion and focus further research and to ground an evidence based WHO perspective and policy on IP and vaccines. As noted above, the work of the UK Commission on Intellectual Property Rights (CIPR) Commission may provide a useful (evidence) base[108].

Intellectual property and access to IP protected vaccine technologies

Sections 2 and 3 of this paper outline a number of relevant aspects of intellectual property as it impacts vaccines and, in particular, how intellectual property impacts access to IP protected vaccine technologies.

[107] Interview with Alejandro Costa, WHO.
[108] See section 3.1 *supra*.

One of crucial issues raised in the opening sections was the impact of know-how on vaccine production. It seems that the difference at the present time between the technical capabilities of e.g. an OECD vaccine producer and an emerging vaccine producer in the developing world make the existence of such a know-how gap rather likely (at least in respect of the newer and more sophisticated vaccines).

> *Is there an important know-how gap between developed and developing country vaccine manufacturers? If there is, what is the extent of it? What can be done about it? What will the impact be in years to come?*

It would appear that, at the moment, the issue of the protection of 'undisclosed test or other data' (e.g. arising from clinical trials) as it relates to 'bioequivalence' type procedures does not arise for vaccines in the same way that it does for medicines. However, this may change in the future.

> *What progress is being made on the issue of "well characterised products" that may permit greater equivalency or "comparability" to be established? What impact will the protection of 'undisclosed test or other data' have on vaccines in the future?*

In terms of the general question of access to IP protected vaccines, it is clear that any or all of the IP rights considered, as well as many other factors, could play a role in determining whether there is situation of monopoly or competition. In terms of a general approach to characterising the IP access situation with regard to vaccines, the following could perhaps be considered:

> *Consider developing a methodology for analysing access to vaccine problems in terms of the various types of monopoly e.g. a patent monopoly, a know-how (including trade secret) monopoly, an 'undisclosed test or other data' monopoly and/or any other pertinent monopoly factors, as well as in terms of the scope of those monopolies. The analysis would of course be dynamic, with different factors becoming more or less important over time, rather than static. Such an analysis should lead to a firmer basis for recommendations for how to attempt to deal with particular access problems when they are encountered and on an ongoing basis i.e. it should assist in anticipating future problems.*

A dynamic situation may result not only from the changes in the situation of the relevant vaccine, for example, it may be that a vaccine patent is granted, or expires, or is revoked, or that a potential competitor develops the necessary know-how to permit vaccine production etc There are broader contextual issues as well. One key issue noted in a number of places above is the 1st January 2005 deadline for all WTO Members (except LDCs) to permit patents for pharmaceutical products to be granted, which will likely have an important impact in terms of anticipation of future problems. Despite the fact that the impact of the TRIPS Agreement alone is not yet fully understood, as noted above in section 2.5, new trade agreements are negotiated with 'TRIPS-plus' provisions. Consequently, for example, a Free Trade Agreement may be concluded which further raises intellectual property protection e.g. permits the extension of vaccine patent lifetimes, or prevents the licensing of a competing vaccine product during the lifetime of the patent etc.

It would be sensible for this methodology to be supported with a number of case studies.

> *The Hepatitis B vaccines case could perhaps be studied, not only in terms of the history of the patented recombinant DNA vaccine but also in terms of the history of the competing plasma derived vaccine, as is outlined in section 3.2 above. Questions posed above included: What would the rDNA Hepatitis B vaccine price history have looked like if Dr Prince had not been stimulated to invent his new plasma derived*

vaccine and transfer the technology to an emerging manufacturer? Assuming that the Korean plasma derived vaccines did indeed provide effective competition to the rDNA vaccine, presumably without that competition the price of the rDNA vaccine would have remained higher for longer? If the rDNA vaccine had not experienced any effective competition then presumably, the classic price history of a patented product might have been seen, only falling significantly after the patents had expired, or in this case, been revoked?

It would also be interesting to substantiate whether or not this (and acellular pertussis) were good examples for the CVI and WHO/WTO documents to have chosen given that there may have been competition in these cases from other vaccines: how unusual is this?

Other examples include the Haemophilus influenzae type B (Hib), meningococcal and pneumococcal vaccines, however, as far as time and resources allow, this methodology could be applied to any selected vaccines of interest.

Is there a clear example to be found of a problem accessing a vaccine where the problem is just (a) a patent; (b) know-how (including trade secrets); (c) undisclosed test or other data?

Another issue raised above is that of the effect of royalty payments, relied on so strongly by the CVI and WHO/WTO documents.

It would be interesting to try and compare the magnitude of the effect on vaccine end price that royalty payments have compared to the lack of free competition. Is it less likely that the massive price reductions of the sort offered by Cipla for antiretroviral medicines in 2001 or by Cheil or Korean Green Cross for Hepatitis B vaccines in 1986 would have occured if Cipla had been GSK's licensee or KGCC Merck's licensee?

Other potentially interesting questions include:

Investigate the impact of the Bolar exception in the field of vaccines. Is it used?

Investigate the effect of patent 'evergreening' in the field of vaccines. Does it happen?

Investigate patent extension/SPCs in the field of vaccines. Are they sought?

Investigate the structure of the vaccine delivery device market to investigate how that market structure differs from the vaccine market per se.

The paper also reviewed some of the measures used to facilitate access to IP protected vaccines. Relevant issues for consideration may include:

Noting for example the work of the UK CIPR Commission, investigate further the effectiveness of the different access measures outlined in this review, which may broadly speaking thought of as including both business models ('respect IP') and public policy models ('respect IP system'), to inform thinking about access to vaccines options.

Can the measures that have been used so far to try to facilitate access to IP protected vaccines such as tiered pricing and bulk purchasing be relied on in the future?

Can tiered pricing be expected to continue to represent an effective access measure in the light of the perceived schedule divergence?

Will procurement processes such as tenders (c.f. the Hepatitis B Task Force event in Indonesia, see section 3.2 above) be effective for new patent protected vaccines in the light of the global patent monopolies that may be foreseen in the post 1st January 2005 world?

How will voluntary licensing models develop? How much technology can e.g. OECD patent owners be expected to transfer with the licence?

Could compulsory licensing provide an effective mechanism for increasing access to patented vaccines? Is it useful as a bargaining tool? How can the issues of know-how be addressed in order to make compulsory licensing effective?

Building on the foundation of the methodology outlined above, with such an investigation future issues could be better anticipated and, if they are thought appropriate, questions such as "What measures could begin to be taken now to help increase future competition" could be addressed further.

In terms of such anticipation, using the example of the MVP-type model discussed above in section 4.6 and using the methodology outlined above it could be found that a vitally important but unaffordably priced vaccine produced by an OECD manufacturer could in theory be produced by a number of emerging producers at a much lower (competitive) price if one technical problem in a new conjugation process could be solved and a one product patent 'overcome'. The analysis of this section would provide the informed position (and perhaps negotiating base) necessary to decide whether to negotiate with the OECD manufacturer (e.g. with an advance purchase commitment), or whether to try to move toward a situation where that manufacturer provides a patent licence to the emerging manufacturers along with the know-how associated with that one conjugation process step, or whether to try to move toward a situation where a compulsory licence could be obtained along with finding a contract research company to provide the necessary missing know-how.

<u>IP and R&D for vaccines</u>

The discussion in section 4.2 above of the incentive effect of intellectual property in terms of the underlying market raised the issue that IP and the TRIPS Agreement cannot be expected to stimulate private sector R&D in every case. In fact the TRIPS Agreement can be expected to stimulate private sector in respect of rich markets, but cannot be expected to stimulate much if any R&D for poor or non-existent markets. The issues of extra incentives for the private sector was therefore touched upon. Public sector R&D and PPP projects were also noted. Some potentially interesting considerations are the following:

Noting for example the work of the UK CIPR Commission, investigate further the effectiveness of intellectual property as an incentive to perform R&D for the health needs of developing countries. This is of course a particularly interesting time for this investigation given the WHA resolution on innovation and the discussions from the workshop could perhaps be fed into that process.

Extra incentives are being provided to the private sector over and above intellectual property- will this be enough to stimulate the necessary R&D? Could it be imagined that instead of providing extra incentives over an IP system that may not be functioning as an incentive, that a wholly new system could be considered?

What is the impact of the Bayh-Dole Act and other relevant developments in the public sector on vaccine research and development? Is it increasing the efficiency of vaccine innovation take-up by the private sector? Is it changing the way that public sector institutions such as universities interact in the vaccine research and development process? Is this desirable, or undesirable? What are the implications for the present intellectual property model of the discussions about creating a public sector entity to provide development and production skills that have previously been the preserve of the private sector?

What progress are the various vaccine related PPPs making? Are their IP policies delivering the expected cooperation? What problems have been encountered? What lessons have been learned? What caused the recommendation for IAVI's IP policy in the independent review? What is the present status of the MVP model?

In the case of HIV/AIDS vaccines it has been suggested that present efforts to develop an effective vaccine(s), whether in the private, public or public-private sector domain, are insufficient and that a new model is needed, based for example on the Human Genome Project. How will the tension between the necessary openness and proprietary information managed?

Again, case studies should perhaps be carried out to support this process of investigation. The Hepatitis B case study discussed above in section 3.2 already seemingly raises a number of important points. If the operation of the intellectual property system is to be well understood in the context of vaccines, not only the R&D stimulated by IP should be examined, but also the R&D that is stimulated without considerations of IP - It seems that Dr Prince's plasma derived Hepatitis B vaccine was invented with no profit incentive in mind, quite the opposite in fact. For a number of different vaccines relevant to the developing world, it would be interesting to study what R&D has been stimulated and, having regard to IP considerations or the lack of them, why?

An issue of immediate importance is the extent to which IP may act as a dis-incentive to R&D or may otherwise block necessary R&D activities.

Investigate further the effect of 'upstream' biotech patenting on vaccine R&D for the needs of the developing world. Is negotiation between different IP holders being successful or are vaccine R&D efforts being blocked?

What is the present status of a H5N1 vaccine in the light of the patent issues?

IP, technology transfer and local production of vaccines

The discussion in section 5.1 above raised some of the mechanisms that the TRIPS Agreement provides to attempt to encourage technology transfer. However, as discussed in section 5.2, it is clear that private sector technology transfer will depend on wider 'business model' considerations than just IP. The TRIPS Agreement cannot be expected to stimulate private sector technology transfer in every case. Even if IP makes private sector technology transfer more likely, that still does not mean that it is likely to happen. Interesting issues to address might include the following:

Investigate further what technology transfer is occurring between e.g. the OECD countries and the developing countries, and/or between the developing countries themselves. Is it all mediated via a for-profit IP framework. If not, what are the alternatives? How much technology transfer of 'core' production technologies (in terms of e.g. know-how including trade secrets) can realistically be expected given

the likely tension between e.g. OECD and emerging suppliers in terms of strategic cooperation vs strategic competition?

Case studies should be carried out to support this process of investigation. The Hepatitis B case study in section 3.2 already seemingly raises a number of important points. It is not clear that Dr Prince's transfer of technology to Cheil in South Korea involved significant IP considerations? How were the other technology transfer processes in that case managed?

What role can the public sector play in effective vaccine technology transfer?

Can the apparent know-how gaps of emerging suppliers be remedied through contract research, development and technology transfer to the emerging supplier, on the basis of an MVP-like model (noted above in section 4.6)?

The issue of technology transfer to the developing world needs to be addressed in the context not only of science and technology base but in terms of local production.

The economies of scale issues (and perhaps quality issues) are taken by some to indicate that, whatever the IP situation, extensive local production of vaccines in the developing world undesirable? What is likely the optimal distribution of vaccine production in the developing world (presumably perhaps varying from case to case) and how can intellectual property help deliver that outcome?