

Intellectual Property Rights and Vaccines in Developing Countries

Meeting report
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Abbreviations and acronyms

ECBS	WHO Expert Committee on Biological Standardization
ADIPs	accelerated development and introduction plans
AIDS	acute immunodeficiency syndrome
AUTM	Association of University Technology Managers
CBER	Center for Biologics Evaluation and Research (US FDA)
CBL	Cambridge Biostability Ltd
cGMP	current good manufacturing practice
CIPR	UK Commission on Intellectual Property Rights
CIPIH	WHO Commission on Intellectual Property Rights, Innovation, and Public Health
CRADA	Cooperative Research and Development Agreement
DCVMN	Developing Country Vaccine Manufacturers' Network
DTaP	Diphtheria–tetanus–acellular pertussis vaccine
DTwP	Diphtheria–tetanus–whole cell pertussis vaccine
EPI	Expanded Programme on Immunization
ETEC	Enterotoxogenic <i>Escherichia coli</i>
EU	European Union
FDA	Food and Drug Administration (USA)
FTAs	free trade agreements
GAVI	Global Alliance for Vaccines and Immunization
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
IAVI	International AIDS Vaccine Initiative
IFPMA	International Federation of Pharmaceutical Manufacturers' Associations
IP	intellectual property

IPPPH	Initiative for Public–Private Partnerships in Health
IPR	intellectual property rights
IPV	inactivated polio vaccine
IVB	WHO’s Department of Immunization, Vaccines and Biologicals
MIHR	Center for Management of Intellectual Property in Health R&D
MMR	measles–mumps–rubella vaccine
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NIBSC	National Institute for Biological Standards and Control (UK)
NIH	National Institutes of Health (US)
NIP	national immunization programmes
NVI	Netherlands Vaccine Institute
OECD	Organisation for Economic Co-operation and Development
PATH	Program for Appropriate Technology in Health
PIIPA	Public Interest Intellectual Property Advisers
PPPs	public–private partnerships
PRP-T	A tetanus toxoid–Hib polysaccharide conjugate
R&D	research and development
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment)
SAAVI	South African AIDS Vaccine Initiative
SARS	severe acute respiratory syndrome
SGS	sugar glass stabilization
SII	Serum Institute of India
SOPs	standard operating procedures
TB	tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UK	United Kingdom of Great Britain and Northern Island
UNICEF	United Nations Children’s Fund
US	United States of America
WHA	World Health Assembly
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

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Finally, we would like to express our gratitude to Daniel Tarantola, who chaired the meeting, and to Charles Clift, Marie-Paule Kieny and Michel Zaffran for their continued support to this effort.

1. Introduction

1.1 Welcoming remarks and objectives

Dr Daniel Tarantola, Director of WHO's Department of Immunization, Vaccines and Biologicals (IVB), moderator of the meeting, opened it on behalf of the Director-General, Dr Lee Jong-wook. In his opening remarks, he noted that WHO as an intergovernmental organization is respectful of international law. Its actions are guided by its governing bodies, the Executive Board and the World Health Assembly (WHA), for which it provides the secretariat.

Dr Tarantola recounted a short history of WHO activities relative to Intellectual Property Rights (IPR) for vaccines, including consideration by IVB's Strategic Advisory Group of Experts in 1997, inclusion in the report of the WHO Commission on Macroeconomics and Health, and the May 2003 WHA resolution on IPR, Innovation and Public Health, resulting in the creation of a commission on the same subject. He introduced Dr Charles Clift, who was the coordinator of the UK Commission on Intellectual Property Rights, which in 2002 produced a document that has become a global reference. Dr Clift is now the secretary for the new WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH). The Commission was set up in February 2004, and its first meeting was 5–6 April 2004. Among the Commission's rules of procedure are openness and transparency, with submissions and publications on a WHO website in the public domain (www.who.int/intellectualproperty). IVB's concern is to achieve global equity in access to vaccines that have a significant public health impact, and this at a cost that is affordable and sustainable over time.

Dr Tarantola noted that this meeting was timely and important, given the current revolution in vaccines in terms of the ever increasing number of antigens and the mounting interest and tension prevailing around IPR. He characterized this meeting as a forum for international exchange to achieve a clearer understanding of the current state of affairs, the issues at stake and the information needs. To this end, a working paper by Christopher Garrison would set the framework for discussion. This meeting would not lead to recommendations to WHO, as the group does not include all stakeholders, such as beneficiaries, Member States and regional interests, but would take note of statements. These would be attributed as far as possible, with longer position statements to be included as annexes to the proceedings. The Secretariat would then write its own synthesis as a contribution to the work of the CIPRH, on which meeting participants may comment.

Dr Tarantola recognized the work of the Access to Technologies team, under the leadership of Michel Zaffran, and especially Miloud Kaddar, who was charged with organizing this meeting. This was followed by the self introduction of participants. A list of participants is included in **Annex 1**. The meeting agenda is in **Annex 2**.

Mr Miloud Kaddar then presented the rationale and objectives of this meeting. He noted that the international debate on intellectual property rights and pharmaceuticals has developed with very few references to vaccines. In addition, the world of vaccines is operating in a changing context, including product divergence across markets, the emergence of developing country manufacturers, who now supply 70% of UNICEF's vaccines in terms of volume, new arrangements being made between the research and development (R&D) based industry and emerging suppliers, the new role of public-private partnerships (PPPs), increasing regulatory requirements and liability concerns, which are raising production costs, and the fact that patent portfolios are becoming a more important component of company assets. Although IPR have not to date been a major obstacle in access to vaccines, they may have a more important role in the future, especially for production of new vaccines and technologies in developing countries. The objectives of the meeting were thus to provide an open forum to update information and to discuss how to move forward in three specific areas: (a) the impact of IP protection on access; (b) directions and options for an appropriate balance between stimulating R&D and enhancing access; (c) informal input to the WHO commission.

2. Setting the stage

2.1 WHO commission on IPR, innovation and public health

2.1.1 *Presentation by Dr Charles Clift*

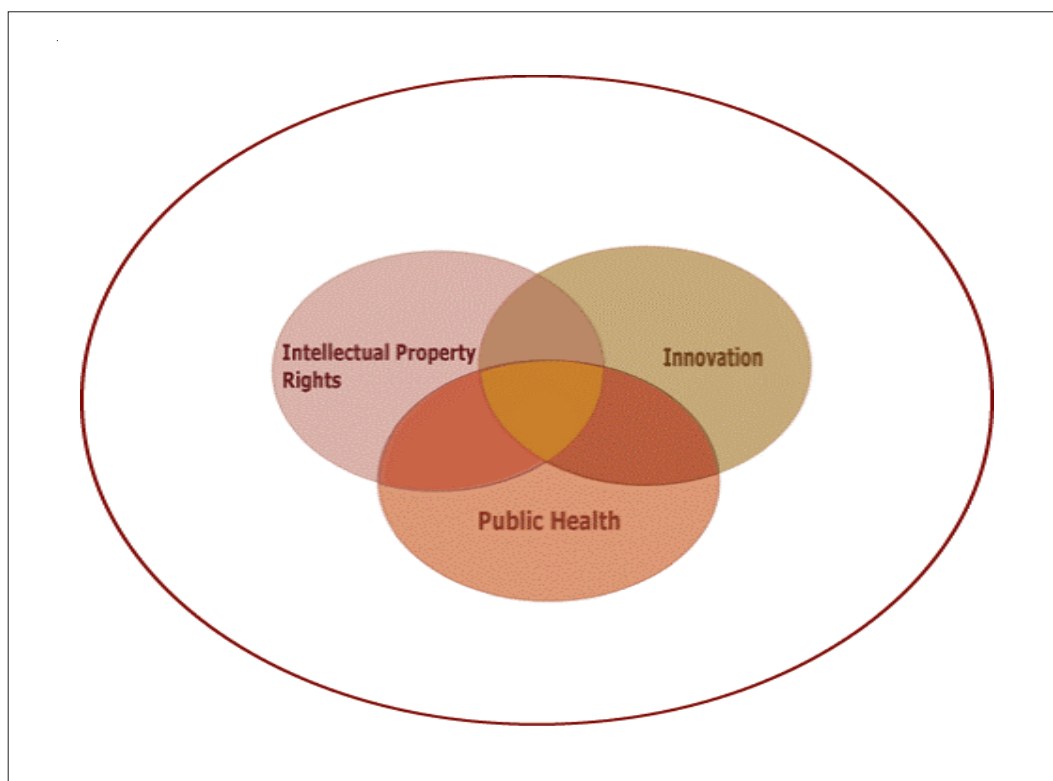
The Commission on Intellectual Property Rights, Innovation and Public Health was created in February 2004 as a result of a resolution (WHA56.27) of the Fifty-sixth World Health Assembly in May 2003. Its terms of reference are:

...to collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries...

More background on the Commission and its members can be found on its website: www.who.int/intellectualproperty.

The priority areas for the Commission are at the intersection of the three major themes of their enquiry as illustrated in Figure 1.

Figure 1: Priority areas of the Commission on Intellectual Property Rights, Innovation and Public Health



A key concern of the Commission is how IPR work to stimulate innovation in the field of public health and how they may relate to accessibility to the products of innovation. But there is a more general concern about the incentives for innovation, of which IPR are only one, and how these incentives might be better tailored to meet the needs of developing countries for medicines and other products to address public health concerns.

While recognizing the important role that IPR play in stimulating innovation in the pharmaceutical (and biotechnology) industry, much of the debate on IPR and public health has focused on the possible impact that patents on final pharmaceutical products have on the prices paid in developing countries and, hence, their affordability. In the case of vaccines, the nature of their development and production and the nature of the final market may require a different kind of debate. Key differences with pharmaceuticals include the following:

- There is a much smaller market for vaccines – the total value of sales is well under 2% of total sales of pharmaceutical products. As with medicines for so-called “neglected diseases”, the small size of the market in total, of which a small fraction is in developing countries, blunts the commercial incentive for undertaking research and development on new products.
- The public sector is very much more involved in production, pricing and marketing than in the case of pharmaceuticals. Public sector purchasers are keen to drive down prices to levels compatible with making vaccines as widely available as possible.

-
- Vaccines are biological rather than chemical products and production processes to ensure quality and potency are often more complex and costly. Similarly, delivery systems (including, for instance, cold storage) are more demanding than for chemical medicines.
 - For similar reasons, clinical trials and obtaining regulatory approval, particularly for new classes of vaccines, may be more costly and time consuming.
 - In the context of IP, copying vaccines may be more difficult or costly than in the case of chemical medicines. The ability to reproduce a production process may depend on tacit knowledge that is not revealed in public documentation such as patent applications.

As noted above, the incentives for vaccine development are limited by the size of the market. Moreover, as compared to pharmaceuticals, the market undervalues the social and health benefits of vaccines, which in the right circumstances confer a benefit to non-consumers over and above that conferred on the vaccinated. Thus the probability that market incentives will result in the socially optimal amount of investments in vaccines is very low. There could be reasons of scientific tractability, but it may be significant that about 15 anti-retrovirals for treating the symptoms of HIV/AIDS have been developed but, as yet, no vaccines against the disease. A declining incentive for vaccine production is indicated by the fact that the number of large pharmaceutical companies producing vaccines in the USA has declined from 26 in 1967 to 4.¹

In addition, many of the institutions working on vaccine development have encountered difficulties of various kinds in accessing or licensing technologies (“research tools”) needed for R&D that are protected by IPR. Since they often work on specific diseases with a limited number of different approaches to reaching their research goals, these obstacles may be more difficult to overcome than in “mainstream” research, where companies may more easily circumvent obstacles by changing their approach to a research problem, or indeed switching to another problem altogether if they cannot easily achieve “freedom to operate”. In this context, the way that the participants use the system, or indeed the rules on patenting research tools, may require examination.

In conclusion, it seems a reasonable hypothesis that the issue of patents on vaccines as end-products and their possible impact on access is different from that in pharmaceuticals. There are fewer current vaccine products that are patented, and the fact that governments (and international agencies) are major purchasers, limits the scope for producers to secure higher prices through exercising their exclusionary rights. Rather, the IP issue is how to ensure that unnecessary disincentives are not put in the way of vaccine developers, either in the process of R&D, or in developing the ability to produce vaccines. Thus the key access problem is the absence of vaccines that could save millions of lives, and millions of dollars of avoided treatments.

¹ The last two sentences derive from the “The costs of developing vaccines: Case study of VaxGen’s HIV Candidate Vaccine” by Donald Francis, presented at the workshop “Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Private-Public Partnerships” held at the Wellcome Trust, London, on 15–16 April 2004.

2.1.2 Discussion of Clift presentation

Dr Roy Widdus noted that, despite the 1.5% share that vaccines have in global pharmaceutical turnover in dollars, vaccines represent much more than 1.5% of the capacity to deal with global public health problems, because they have positive externalities. Therefore, it will be important to break the cycle in which the perceived value of vaccines is decreasing. Dr Jerry Sadoff responded that in the next 10–20 years, the market for vaccines in developing countries will be US\$25 billion for vaccines with IP protection, but only US\$5 billion for those without it; thus IP preserves investment. IP is critical for development as well as for future price. He noted his calculations were based on vaccines assumed to be developed in the next 5–10 years, and on the prices for generic vs R&D protected-vaccines.

Dr Harvey Bale suggested that comparisons of the market size of vaccines imply that the large multinational pharmaceutical companies are not interested in developing vaccines. This is not true. A major reason for the disparity in market size is the difficulty of science.

Professor Isaias Raw wondered how much money for vaccine R&D comes from the private as opposed to the public sector. Dr Alan Shaw responded with two examples, for rotavirus and human papillomavirus (HPV) vaccines. He said that with clinical studies being funded by the private sector at approximately US\$3000 per patient, and about 70 000 patients, the private sector investment of over US\$200 million far outweighs the public sector research investment, which is US\$100 000–US\$900 000.

Dr Clift responded that his argument was not that IP protection was not important for vaccine development, but that the issues were somewhat different to those discussed in respect of pharmaceutical development. The decline in the number of large companies involved in vaccine production, quoted in the presentation, seemed to be incontrovertible evidence that there was a problem of incentives for the private sector.

2.2 Review of previous WHO documents, new developments and issues

2.2.1 Presentation by Mr Christopher Garrison

Below is a summary of some of the issues presented to the meeting by Mr Christopher Garrison and provided in a background paper. These centred on the relevance to vaccines in the developing world (or expected relevance) of the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. Please see **Annex 3** for a list of bibliographic references compiled by IVB, and **Annex 4** for a statement on the working paper submitted after the meeting by the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA).

The purpose of the presentation was to stimulate debate and encourage the gathering of evidence to form the basis of further discussion and analysis. A number of previous documents were reviewed that outlined a general hypothesis that IP can be expected to encourage R&D and stimulate technology transfer (subject to certain caveats) and that it has not generally been shown to be a significant barrier to accessing present vaccines. In the context of the operation of IP in the developing world, however, it seems that some further qualification may be necessary.

There have been some notable developments since, in particular, the earlier documents reviewed, including the “access to medicines” debate, leading to the WTO Doha Declaration on TRIPS and Public Health (14 November 2001), reconfirming the public health related “flexibilities” of the TRIPS Agreement, including compulsory licensing. The UK Commission on Intellectual Property Rights (CIPR) delivered an influential report (September 2002) on the role and impact of IP in the developing world. The recent WTO Decision of 30 August 2004 created a new legal mechanism to overcome an outstanding problem identified in the Doha Declaration, relating to the inability of WTO Members without adequate manufacturing capacity to make effective use of compulsory licensing for pharmaceutical products. Newly negotiated “free trade agreements” (FTAs) will very likely reduce the ability of the developing country parties to make use of the TRIPS flexibilities.

There are a number of IP rights that are relevant to vaccines although the differences between vaccines and medicines mean that the way in which IP impacts the two will likely be different (other strongly relevant issues such as regulatory requirements, market structure, liability issues and the scientific and technical challenges were not covered in this presentation).

A wide range of vaccine-related inventions are now patentable, ranging from “upstream” research-related inventions to “downstream” product and delivery-related inventions. Different patents or portfolios of patents relating to the same vaccine may be owned by different parties. “Know-how” is a more important factor for vaccine production than for (small molecule) medicine production. There is a marked know-how gap between OECD vaccine producers and emerging vaccine producers. “Trade secrets” may form a specific subset of know-how. There is related protection in the TRIPS Agreement for “undisclosed test or other data,” relating to clinical trial data submitted to a regulatory authority, for example. Although the issue of a generic medicine obtaining regulatory approval without the need to carry out clinical trials through “bioequivalence” procedures is well known, this has yet to happen for vaccines given that the nature of the vaccine production process does not yet permit an equivalent comparison and so each vaccine manufacturer has to submit their own clinical trial data to obtain licensure.

A key patent concept is “monopoly vs competition”. Patent monopolies are inherently limited. Competition to a patented product may be possible during the lifetime of the patent, and will occur after the patent has expired. The most substantial issue with respect to access to a patented vaccine will arise if there is no competition during the lifetime of the patent, in which case the patent owner may have significant freedom to price the vaccine in a way which would maximize their return on investment (profit). Such pricing is different from that which maximizes access to that vaccine for all those who need it. The limitations on patent monopolies include limitations on scope (it may be possible to use a different technique which is not protected by the patent to achieve the same effect, or a sufficiently similar effect to using the patented invention), limitations on geographical extent (patents are granted on a country-by-country basis and competition may therefore occur in countries where the relevant patent has not been granted), and limitations on the lifetime of a patent (the TRIPS Agreement provides that a patent may last for at least 20 years from the filing date although some countries extend this period to make up, for example, for delays resulting from the regulatory process in terms of the product on the market). Countries used to have the freedom to decide whether or not to grant patents for medicine and vaccine-related inventions. However, in a

relatively short period of time from the entry into force of the TRIPS Agreement (up to 10 years, the deadline being 1 January 2005) all developing countries will have to change the law to permit the granting of these patents, if they have not already done so (least developed countries have until 2016). Royalty rates in patent licenses may be important but are probably not as significant a factor in access considerations as lack of unfettered competition.

Actual or potential mechanisms to facilitate access to patented vaccines include:

- tiered pricing (the fact that there has been little possibility for “parallel importation” of vaccines given the cold chain distribution system, unlike the situation with medicines, has likely facilitated tiered pricing; however, there may now be a threat from schedule and market divergence);
- bulk purchasing (procurement of “new” vaccines, especially, for example, in an open tender, will likely be increasingly impacted by IP issues post-TRIPS);
- voluntary licensing (apart from the traditional business case circumstances, given changes in the private, public and public–private sectors, there are now a number of new and more sophisticated paradigms for IP licensing and management); and
- compulsory licensing (at least one compulsory license relating to vaccines has been granted, in Israel, but in general a lack of the relevant know-how for vaccine production may likely limit the effectiveness of compulsory licensing).

The extent to which IP may have impacted access to existing vaccines is not completely clear, but it does not seem to have been a predominant factor. It seems fair to suggest that IP is likely to be more of an issue in terms of access to new and future, IP protected, vaccines.

Both the public and private sectors have been investing resources in vaccine R&D for the developing world, but at a level which is to date insufficient to match the need. The amount of R&D that can be expected to be stimulated by IP will vary with the viability of the relevant market. In a rich market, IP rights will be valuable and private sector R&D will be stimulated. In a poor or non-existent market, IP rights will not be valuable and little or no private sector R&D can be expected to be stimulated. Private sector vaccine R&D for the needs of the developing world may be further stimulated by extra incentives, over and above IP. Following the Bayh-Dole Act, IP now plays a greater role in public sector vaccine research than previously. A challenge will be to resist the public sector’s dealing with IP in the same way as the private sector, for example to maximize income rather than maximize public health benefit. Public–private partnerships have become a tremendously important concept in vaccine R&D, with new IP arrangements holding out the possibility of both sectors contributing their own strengths to obtain a public health outcome that neither could have achieved alone. The concept is still in an investigatory phase, however.

There are circumstances where IP may act as a disincentive to R&D. There may be problems with broad, fundamental IP rights (potentially blocking follow-on innovation) or with many IP rights relating to a given target being granted to different owners (leading to patent “thickets”). Possible solutions lie in patent licensing (perhaps patent “pooling”) whether voluntary or compulsory.

The TRIPS Agreement has provisions to encourage technology transfer but this cannot guarantee that it will take place. Private sector technology transfer will depend strongly on business case considerations. An interesting PPP model involving technology transfer is that of the Meningitis Vaccine Project (MVP), utilizing contract R&D and technology transfer of the results to an emerging vaccine manufacturer. There remains debate about the merits or otherwise of local vaccine production and hence the appropriate role of technology transfer.

What we all aim for, with TRIPS and other measures, must be to provide an effective vaccine innovation system, stimulating the vaccine R&D necessary for the developing world *and* providing timely and effective access to the new vaccines produced for all those in need.

2.2.2 Discussion of Garrison paper

Mr Charles Caruso stated that the paper adopted a biased view of the IP situation insofar as patents are not applied for uniformly in all countries – in fact, his company, Merck, has applied for few patents in less developed countries. Merck has developed 12 vaccines and the patent situation is different for each. Mr Garrison replied that naturally this is the case – when he was a corporate patent attorney, his company would choose where to file for patents based on the market at hand. Since patents are expensive to obtain, a company will likely file only where they need to exercise control of the market. Patents in rich countries and upper tier developing countries such as India where potentially competing producers are based can perhaps be expected to be more valuable for the exercise of control over a market than patents in the poorer developing countries.

Mr Caruso also noted that in filing a patent, its scope must be defined. Mr Garrison agreed, but added that there have been some overly broad patents, particularly some related to gene fragments, although action has now been taken to address this issue.

Mr Pedro Roffe raised an issue related to the provisions of one of the “TRIPS plus” FTAs (between the United States and Central American countries) that links marketing approval to patent rights. He wondered if the requirement for the sanitary authority to review patent rights might nullify the Doha Declaration on compulsory licensing. Mr Garrison stated that there is a lengthening list of FTAs with the USA, which narrows national flexibility. However, he suggested that it should be possible for national legislation to be designed so that this provision does not stand in the way of effective compulsory licensing according to a European Union (EU) position.

Dr Bale spoke in favour of TRIPS-plus agreements as also being access-plus, because countries signing such agreements with the USA are getting access to a very large market. Dr Jean Petre expressed concern that compulsory licensing is the result of unresolved litigation. Mr Garrison noted that compulsory licensing is often used as a negotiating tool by both developing and developed countries.

Professor Raw reiterated his concern about moral and public health issues. He suggested that manufacturers running clinical trials on products in the developing world should pay the country for this right, or should provide access to the product.

3. Intellectual property and access to vaccines

3.1 Role of IP in the development and introduction of vaccines in developing countries

3.1.1 *Presentation by Dr Richard Mahoney*

Intellectual property protection is valuable for both the public and private sectors. It has long been recognized that IP is valuable to the private sector because it allows for the recovery of investment necessary for innovation. However, it has not been well understood how or whether IP benefits the public sector. Indeed there has been extensive controversy on this topic with some arguing that IP limits access to drugs for the poor in developing countries. IP is of significant value to the public sector because of the need to mobilize funds to cover the costs of passing through the drug regulatory process. Drug regulatory procedures reflect the wishes of the general population as expressed through democratic processes. Simply put, individuals want that they and their children receive safe and effective drugs and vaccines. Under our current system, IP provides protection to investors who are willing to provide the funds necessary to bring a product through the regulatory process to licensure and availability. These investments therefore are of great interest and value to the public sector.

Unfortunately, there is a very little scholarly research on the relationship between IP and access to drugs and vaccines by the poor in developing countries. To address this lack, the Centre for Management of IP in Health R&D (<http://www.mih.org>) has undertaken a case study on the impact of IP on the availability of hepatitis B vaccine in developing countries. Hepatitis B vaccine can be produced in two ways: either by extracting the hepatitis B surface antigen (HBsAg) from plasma of individuals who have been infected by the hepatitis B virus; or producing HBsAg in genetically modified yeast cells (e.g. *Saccharomyces cerevisiae*). Today most of the vaccine used in the world is produced by the latter method.

When plasma-derived hepatitis B vaccine first became available in the late 1970s, its price was in excess of US\$ 18 per dose, which was beyond what the poor in developing countries could afford. In the early 1980s, the recombinant DNA version of the vaccine came on the market and it too was priced at levels beyond the ability of the poor in developing countries to afford. Thanks in part to the efforts of the International Task Force on Hepatitis B Immunization, the cost of plasma-derived hepatitis B vaccine fell to less than US\$ 1 per dose. However, the cost of recombinant DNA hepatitis B vaccine remained relatively high compared with the plasma-derived product. Eventually, in the late 1990s and early 2000s the cost of the recombinant product fell precipitously and is now available at less than US\$ 0.30 per dose.

The MIHR research indicates that there are three core patents for the production of recombinant DNA hepatitis B vaccine. These are patents assigned to the Pasteur Institute in Paris, Biogen in the Netherlands and the Regents of the University of California. These patents were filed only in the USA, Europe and a few other countries. In addition to these three core patents, there are a very large number of other related patents having to do with isolation, purification and other aspects of vaccine production. The Pasteur patent was issued on 29 August 1980; the Biogen patent on 31 March 1982; and two University of California patents were issued on 21 June 1988 and 7 June 1995. The two major international companies – Merck & Co. and GlaxoSmithKline (GSK) – producing recombinant DNA hepatitis B vaccine had licenses to these three patents. In the mid-1990s, two vaccine manufacturers in the Republic of Korea introduced recombinant DNA hepatitis B vaccine. One of these companies obtained the know-how for production of the vaccine from one of the organizations that has been licensed by the University of California under its patents. The other company obtained its know-how and intellectual property rights to a new method of production of hepatitis B vaccine using a different the strain of yeast (*Hansenula polymorpha*). This methodology was developed and patented by RheinBiotech of Germany and transferred to the Republic of Korea through a joint venture agreement. Both of these approaches were within the IPR laws because the three core patents had not been filed in the Republic of Korea and the Korean manufacturers did not seek to commercialize their vaccines in countries where the patents have been filed. In fact, the MIHR study concludes that the Korean manufacturers would not have sought to commercialize their vaccines in the USA or Europe even if the patent barriers had not existed. The cost of obtaining US Food and Drug Administration (FDA) approval and the difficulty of entering the US and European markets were beyond the financial resources of these companies.

Of particular importance in this analysis is the issue of vaccine regulation. The Republic of Korea FDA had not achieved a level of capability that met the guidelines of WHO, which was not prepared to provide “prequalification” status to the Korean products until the Korean FDA was upgraded. WHO provided technical assistance to the Korean FDA, and the FDA, itself, undertook the required effort to meet WHO guidelines. A second factor was the absence of a large international public sector marketplace for the Korean vaccine. With the establishment of the Global Fund for Children’s Vaccines (now called the Vaccine Fund) with an initial donation from the Bill and Melinda Gates Foundation, these resources became available and initial procurements caused the price to drop dramatically.

Based on this analysis, the research leads to the conclusions that IP was only one factor in determining the amount of time it took Korean manufacturers to enter the marketplace and provide recombinant DNA hepatitis B vaccine at very low prices. This conclusion led the study to seek the key determinants for development and introduction of new vaccines into the marketplace, particularly into developing countries. There are six determinants: support for vaccine R&D, development of biotechnology manufacturing capability, creation of domestic markets, creation of export markets, development of systems to protect IP, and creation of systems for vaccine regulation. The availability of vaccines in developing countries is a result of a dynamic interplay among the six determinants. With respect to the particular case of the availability of recombinant DNA hepatitis B vaccine from Korean manufacturers, the most important issues were regulation and market development.

The management of intellectual property issues can be very complex, take a great deal of time and be quite expensive. However, it is probably the case, at least with respect to vaccines, that although IP is an important and complex barrier it is not an insuperable one.

3.1.2 Discussion of Mahoney presentation

Dr John Wecker cited the case of rotavirus vaccine, a live oral attenuated vaccine, where IP is not an issue. However, lack of IP does not guarantee access where there is no market. Data on burden of disease need to be generated and understood by countries. Dr Sadoff agreed, but noted that IP may be a solution. He suggested a simple rider on licensing agreements that companies that license the vaccine for commercial use must make it available at cost-plus for the developing world. Relating to the ability to include such terms in patent licenses and in particular so-called “march-in” rights, Mr Garrison cited the specific case of Norvir, an anti-retroviral drug, as a possible test case. Dr Mark Rohrbaugh reminded the participants that in the case of research supported under the Bayh-Dole Act, there is no legal means to require recipients of US Government funding to set prices for technologies so developed.

Dr Shaw tried to put the hepatitis B vaccine discussion into a historical context, using his “retrospectascope.” He noted that hepatitis B vaccines were originally targeted at high-risk groups, not for universal use. If the public health thinking had evolved sooner, the funding structure might have been very different. Dr Mahoney added that we are now living in a different world with respect to resources available to the public sector. He said the real challenge now is effective “management” of IP.

3.2 Additional IP parameters affecting access

3.2.1 Presentation by Dr Martin Friede

The objective of this presentation was to highlight the fact that many components and technologies go into making a vaccine, and each of these may be subject to intellectual property. Developing a modern vaccine may therefore require access to multiple IPs, and multiple license agreements.

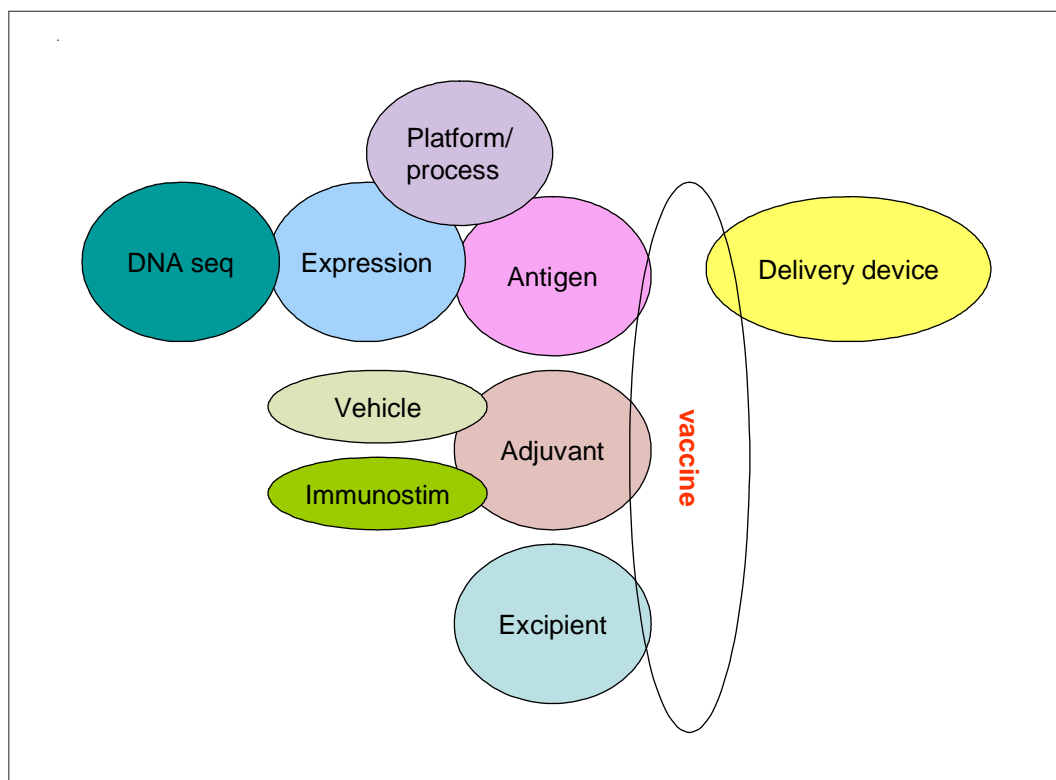
This is particularly true for recombinant or subunit vaccines, where in addition to the antigen and vector platform, a variety of technologies are required to express and purify the antigen, and to formulate it so that it is immunogenic, induces a protective immune response, is stable and can be appropriately delivered. IP on cross-cutting technologies such as expression systems, fusion partners, immunostimulators, adjuvant systems, excipients and delivery devices may be required, and access to each IP component may limit the feasibility of making a vaccine. This is represented in Figure 2.

A variety of IP management situations result that may impact access to vaccines. For example, when cross-cutting technologies are used, such as adjuvants or delivery devices, new IP on the vaccine containing such additional features increases the patent lifetime on the vaccine, and can be used to provide increased territorial protection if the IP on the components was territorially limited. Thus modern vaccines, even if based on antigens which are in the public domain, may be protected by IP on

a component of the vaccine. Development of an equivalent vaccine by an alternative manufacturer may be limited by access to a license for a single component technology, as well as by the R&D and regulatory capacity required to demonstrate equivalence.

As another example, if a particular immunostimulant is able to render an antigen protective, yet the immunostimulant has been (co-)exclusively licensed to parties who are not developing vaccines based on that antigen, this can prevent that antigen being effectively developed.

Figure 2: IP parameters to vaccines



3.2.2 Discussion of the Friede presentation

Dr Wecker noted that IP issues would be very important for others besides OECD manufacturers, such as research institutions and developing country manufacturers.

3.3 Intellectual property and avian influenza vaccines

3.3.1 Presentation by Dr Magnus Schoeman

Dr Magnus Schoeman gave a presentation on IP issues arising in the development of avian influenza vaccines. The National Institute for Biological Standards and Control (NIBSC) is a non-departmental public body sponsored by the United Kingdom's Ministry of Health, but it is kept "at arms length" and is somewhat independent. Its role is assuring the safety of biological medicines in two ways: (a) batch release as an Official Medicines Control Laboratory and (b) development of reference materials used in the biological assays for control testing. In addition, a very active research programme underpins these activities. NIBSC is facilitating collaboration between WHO collaborating centres, national regulatory authorities and manufacturers to

produce candidate H5N1 vaccine strains by reverse genetics and to resolve obstacles to the manufacture and licensing of vaccines prepared by this technology. The goal of this collaboration is the preparation of a small number of candidate vaccine strains that could be made available to all manufacturers of influenza vaccines in the event of the need to produce H5N1 vaccines to combat a pandemic. NIBSC has some experience in generating high growth reassortant influenza viruses using the 12 plasmid reverse genetics system and is currently generating an H5N1 reassortant virus on Vero cells that have previously been approved for vaccine production. Any H5N1 virus resulting from this work will be characterized by WHO collaborating centres and may be used to develop a vaccine for clinical evaluation.

The presentation covered the main intellectual property issues encountered in the above activities. The underlying reverse genetics technology is covered by a number of patents (including the following “Palese” US patents, Nos. 5 166 057; 5 820 871; 6 001 634). NIBSC has sought to ensure that the appropriate rights are in place so that development of a vaccine based on H5N1 is not hindered. In addition to getting permission from patent owners, this has also involved the negotiation of agreements associated with the transfer of biological materials (plasmids and cell lines). Good cooperation, from both institutes and industry, has meant that NIBSC are now in a strong position to provide a candidate vaccine strain should the need arise. However, there are still unknown questions. For example:

- Will strains developed by reverse genetics be readily adopted as seeds by vaccine manufacturers?
- Will strains developed by reverse genetics lend themselves to manufacture on an industrial scale?
- Will strains developed by reverse genetics be effective in providing protection of the human population?
- How will the world’s government authorities review and respond to strains developed by reverse genetics (e.g. in terms of release into the environment)?
- What additional benefits will reverse genetics offer in developing seed strains and which of these benefits will be most tangible?
- What will be the best way of ensuring that patent holders are recompensed for access to their intellectual property?
- What alternative technologies to reverse genetics are there and will these play a role in vaccine development?

3.3.2 Discussion of Schoeman presentation

Dr Widdus wondered about the incremental costs of working around a situation where a piece of IP was lacking, suggesting that it was relatively low compared to overall vaccine development expenses, including investment in facilities. Dr Sadoff agreed that the cost was low, but noted that it lengthened the development timeframe and added uncertainty, thus increasing its impact on costs.

Dr Mahoney asked about the effort to develop new IP in the influenza situation, noting that the Korean manufacturers (of hepatitis B vaccine) had aggressively developed their own IP. Dr Friede said that most companies were working on this strategy as a negotiating tool. Dr Schoeman agreed that this was possible in theory but public health organizations have focused remits.

There followed more discussion on whether IP problems could be solved through negotiation. Mr Garrison said that a large patent portfolio was helpful in the negotiation process but that, of course, having a large patent portfolio was more likely to be the case with a multinational pharmaceutical company than, for example, a start-up biotech firm. Dr Rohrbach said the interest of the National Institutes of Health (NIH) was to maximize the public health benefit, and more than 80% of their licenses were non-exclusive. Dr Friede described a case where a biotech company needed an exclusive license from the NIH to protect its investment, and its unavailability thus stopped development. Mr Caruso pointed out the importance of resolving issues when possible, but also of innovating around patents. Dr Mahoney said that this was exactly what happened in the Korean hepatitis B vaccine example.

3.4 MVP three-pillar approach to access, R&D and technology transfer

3.4.1 *Presentation by David Daout*

Mr David Daout presented a case study of the Meningitis Vaccine Project (MVP) and how it had accessed a particular technology essential for their product. There were three parts to the agreement:

- *A Cooperative Research and Development Agreement (CRADA) with the FDA/Center for Biologics Evaluation and Research (CBER).* The MVP team met with FDA/CBER at the end of June 2003 to begin negotiations and drafting of the CRADA. The objective of the CRADA is to transfer technology for a high yield group A meningococcal polysaccharide tetanus toxoid conjugate vaccine.
- *Training for technology transfer.* While waiting for official approval, the business development team negotiated the start of technology transfer in early December 2003 with a visit from two scientists from the Serum Institute of India (SII). At the same time MVP signed a confidentiality agreement and a material transfer agreement to be able to send raw material to FDA/CBER. MVP catalysed and participated in successful technology transfer of the CBER conjugation technique to SII scientists in December 2003 and provided technical and financial support to this vaccine development. The three-week technology transfer training for SII at the CBER laboratories in Washington DC, included verification of all standard operating procedures (SOPs) for process development and analytical methods, demonstration of techniques, replication of the CBER methods by SII scientists, production of six lots of the tetanus toxoid-polysaccharide A conjugate, and definition of analytical methods. Following the training, SII scientists successfully reproduced and scaled up the conjugation method at the SII laboratories in Pune, India.
- *License with NIH.* MVP successfully negotiated a license agreement for the CBER conjugation technology with the NIH (signed in February 2004). The PATH-NIH license agreement grants a license covering two patents related to conjugate meningococcal vaccines. The first is the NIH patent application submitted in August 2003 to cover the CBER technology mentioned in the CRADA “A rapid, high efficacy conjugation method for production of Polysaccharide-Protein conjugate vaccines”. The second is a patent submitted in 1999, “Conjugate vaccines for *Neisseria meningitides*”. The licensed fields of use are “Conjugate meningococcal vaccines”, with territory identified as low- and middle-income countries as defined by the World Bank.

This approach provides a possible model for other partnerships, which includes a North–South transfer of technology, a South–South transfer of a needed vaccine product for developing countries, and a capacity-building approach.

3.4.2 Discussion of Daout presentation

Dr Rohrbaugh noted that this was a good partnership, and an example of how one might enter into a more complex multinational agreement.

Mr Kaddar asked about previous MVP experience with an Italian company, to which Mr Daout answered that it did not work out because of issues of know-how, IP and transfer to a developing country, but that failure brought seeds for success, as they have now a technology with a very good yield and partners who understand the mission better.

Mr Kaddar, noting that the MVP project was well-defined and uncontroversial, then asked how its success or failure would impact other PPPs. Mr Daout remarked that MVP realized its activities were in the limelight and thus were very cautious, but reiterated that the project was on track, with good partners.

4. Intellectual property, vaccine production and technology transfer

4.1 Transfer of technology: OECD vaccine industry perspectives

Dr Pierre Fournier made the presentation on behalf of the IFPMA Biologics Group. He noted the following:

- Industry continues to seek innovative ways of ensuring that an adequate supply of safe and effective vaccines is available to help meet the world's needs. Technology transfers have been suggested as an additional way to help ensure a sufficient supply of vaccines for the world's needs.
- A wide range of health-related technologies can be transferred to developing countries. Local production of biologicals is just one example of technology transfer.
- Patents have not been shown to impede access to existing or "new" vaccines: patents do not prevent competition, and in many developing countries, vaccine coverage is still very poor for non-patented vaccines (e.g. EPI vaccines).
- Rather, impediments to access in developing countries include a range of issues related to infrastructure (cold chain and other), long-term forecasting, finances, political choices, capacity building and others. Industry also faces some impediments related to increased regulatory review times, increasing requirements for compliance with safety and efficacy standards, global variations in regulatory approval requirements, and skyrocketing R&D costs.
- Therefore, the role of technology transfers in addressing these concerns will be limited, but nevertheless important. To be truly viable, a successful technology transfer must have a very strong rationale. Case-by-case analysis is necessary to assess feasibility and chance of success.
- Technology transfers for biologicals present a high degree of technical difficulty. Experience demonstrates that technology transfers can be difficult to complete and can fail to accelerate vaccine availability, reduce production costs and allow for sustainable production over time. In addition, there are minimum conditions for consideration of technology transfers, which include compliance with GMP standards, existence of a strong and independent local regulatory authority, and respect for current WTO and TRIPs agreements.
- Examples of truly successful technology transfer are rare. Current examples between developed and developing countries include partnerships for DTP combinations.
- Above all, technology transfer must be based on a sound rationale, consider realities of local markets and derive good value for all stakeholders.

4.2 Perspectives from the DCVMN

The president of the Developing Country Vaccine Manufacturers Network (DCVMN), Dr Suresh Jadhav, noted that the DCVMN is a voluntary public health driven alliance of vaccine manufacturers from developing countries, aiming to provide a consistent and sustainable supply of quality vaccine at an affordable price to developing countries. The group is made up of state-owned producers and private producers, both large and small. Some member companies are already able to produce high quality vaccines suitable for both local markets as well as for sale to UN agencies, including UNICEF, the Revolving Fund of the Pan American Health Organization (PAHO), WHO and the Vaccine Fund. Most of the organizations are expanding their capacities and adding new technologies including combination vaccines based on diphtheria–tetanus–wholecell pertussis vaccine and *Haemophilus influenzae* type b (Hib) vaccine, and have R&D efforts toward rotavirus, pneumococcal, and other vaccine needs.

With regard to the DCVMN position on vaccine access, Dr Jadhav noted that many developing countries regard the absence of protection as necessary to promote access to drugs at competitive prices. He said that implementation of the TRIPS agreement may lead to high drug prices, low access and a weakening of national pharmaceutical industries. In the 1970s, many European countries were not giving patents on pharmaceutical products. Today, accessing intellectual property is a major factor in the product development cycle. The impact of patents on technology access will now spread to most developing countries as they join the World Trade Organization and thus agree to uphold TRIPS provisions. It is not possible to predict the full impact of TRIPS on vaccine development costs. However, vaccine development requires not only the patentable technology but also the know-how to consistently produce a safe and effective biological product. It is this dependence on know-how, not covered under TRIPS, which may attenuate its impact.

Of real concern to the DCVMN are the unknowns. For example, several patents already in place may impact them: a patent on the use of aluminium phosphate in manufacturing of combination vaccines, although this adjuvant has been used for several decades; cross-flow filtration for concentration has been patented for manufacturing of Hib vaccine.

Dr Jadhav noted that intellectual property rights are complicated and difficult to deal with for many developing world vaccine producers. Manufacturers have identified specific general assistance from which all could benefit including development of template documents for IPR agreements for use by vaccine manufacturers in developing and middle income countries; access to unbiased legal review; assistance in the writing of patent applications; training on how to better detect and understand infringements. He suggested identifying and securing the services of a team of highly qualified intellectual property specialists and/or an institution that has this expertise in house; plus sponsoring and arranging a meeting for all manufacturers to better understand the effect WTO 2005 will have on vaccine manufacturing and supply for use in developing countries. He said that DCVMN expects WHO and other international organizations to take the lead, including developing a white paper to guide how the DCVMN can continue to contribute to the global vaccine picture after 2005.

4.3 Technology transfer issues

Dr Petre provided a third view in the session. He said that vaccine production in developing countries has been characterized by a constellation of state-owned institutes, a network of “Pasteur Institutes,” which is a result of the early version of technology transfer or sharing. The largest countries have created their own national or provincial institutes, to establish self-sufficiency while limiting the outflow of foreign currency, and a few private vaccine or biotech establishments have grown to visible size. The international presence of these institutes is regulated by a system based only on quality: WHO “prequalification” for the supply of vaccine to UN agencies. Few institutes in developing countries have achieved or are likely to achieve prequalification in the near future, as surveys of DTP producers (WHO 1996, 1998) have indicated. EPI vaccines have thus been supplied mainly by the large manufacturers installed in the industrialized world. As a result of mergers and acquisitions of major vaccine manufacturers into larger pharmaceutical conglomerates, resources are shifting to high-margin innovative vaccines, competing with pharmaceutical blockbusters for R&D budgets. In the future, vaccine supply in general and EPI in particular will increasingly rely on capacities in developing countries. This observation has contributed to the ongoing wave of technology transfer in the form of agreements organizing market access as a return on the technology transfer investment itself.

The first exposure of vaccine manufacturers located in developing countries to IP issues was provided by the introduction of recombinant hepatitis B vaccines and their inclusion into the EPI. Several recombinant vaccines were developed (notwithstanding the patent rights acquired by Merck, Sharpe & Dohme and GSK) in countries where patents had not been filed or in territories that were not TRIPs compliant. This was just an extension to human vaccines of a pre-existing concept of “territorial escape” to IP rights. Territorial escape is in principle the opposite of technology transfer: it uses publicly-available information and eventually “know-how” from the ill-defined border between public and proprietary information, without consent of the rightful owner. It may appear as technology transfer through the involvement of institutions or businesses targeting this opportunity. As a paradoxical result, it is now easier to find a source of recombinant hepatitis B vaccine than a DTP vaccine of adequate quality.

Territorial escape creates the following issues:

- eventual distribution of products from “no-patent” countries by various channels including UN agencies, to territories where they infringe IP rights;
- complication of relations between potential licensors and licensees in developing countries;
- territorial escape is in principle destined to disappear by 2005, when all developing countries (except the least developed countries) must provide patent protection to pharmaceutical products (TRIPs compliant). This is another component of future technology transfer. Then, other than ethical exceptions recognized by the international community, manufacturers in developing countries will have to select one of the following options:

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- forget new, proprietary vaccines or wait until patents expire;
 - form licensing and technology-transfer agreements with the innovators; and
 - develop new technology: freedom of action using non-infringing processes.

The first option amplifies the concept of “divergence” where the industrialized world and the developing world gradually cease to use the same vaccines. This is an unstable situation: GAVI funding has shown that, resources permitting, there is a universal demand for the most recent vaccines.

Many examples of licensing and technology transfer agreements are now at various stages of progress. A number of these agreements contemplate the filling and finishing of vaccines from active ingredients supplied by the licensor, sometimes with mid-term or long-term provisions to develop the production of active ingredients. A few projects are already dedicated to the production of active ingredients for present (hepatitis B) or future EPI vaccines (Hib and other glycoconjugates, measles and measles–mumps–rubella [MMR] vaccines), or non-EPI products with a high market potential (influenza, rabies vaccines). These projects are unfolding mainly in the largest countries (Brazil, China and India). These countries (also very active in territorial escape approaches) are potentially closed markets: they raise customs tariffs or cease to grant import permits when domestic production becomes available. Thus to develop or simply maintain access to these huge potential markets, local primary bulk manufacturing (not just secondary filling operations) is a must.

Other developing countries follow a closely related path (e.g. Algeria, Argentina, Egypt, South Africa, Thailand, Viet Nam). State institutes have a domestic market privilege. Closing these institutes because they cannot deliver new vaccines is anathema. This paves the way for PPPs where the licensor supplements the technology and product range of local manufacturers, in return for privileged or exclusive market rights. Vaccine combinations based on locally-produced DTP and more recently developed antigens (e.g. hepatitis B, Hib) provided by the licensor are examples. From the licensor’s perspective, technology transfer is motivated by one single reason: increased or at least sustained profitability. This can provide different scenarios, which are not mutually exclusive:

- relocating the manufacture of less profitable products to shift domestic capacity to more profitable products;
- developing a manufacturing capacity in emerging markets, rather than increasing domestic production; and
- developing a manufacturing capacity in closed markets.

Technology transfer and licensing agreements happen only when there is a reciprocal share of interests and of decision power in the collaboration. Otherwise agreement proposals tend to be one-sided, which complicates relations between the parties. They usually include several or all of the following provisions.

By the licensor: New products initially in finished form, then phased transfer of the corresponding technology; specific and general services for upgrading manufacturing activities, quality systems, logistics, etc.

By the licensee: Respect and service of IP rights: upfront and milestone fees, royalties, exclusivity, no competition; limitation of export territory for the new products; controlled pricing policies for the new products in the territory; provision of adequate resources, particularly human resources: talent pool.

The backbone of such agreements is the tradeoff of technology against territorial privilege. Even when the licensee is a private organization, territorial value results indirectly from import control policies. This general shape endows a noticeable bias: while market privileges for imported products are usually immediate, technology transfer is inefficient or non-existent. The licensor usually has an interest in delaying technology transfer and extending sales of finished products, but deficiencies on the licensee's side are often involved: overestimation of capability, underestimation of "peripheral" activities such as quality operations. This is changing with the need (now recognized by industrialized country licensors) to relocate activities. This mechanism enables the indirect control of supplies by licensors. It is unlikely to significantly diversify the availability of new vaccines, causing instead an extension of market-controlled and IP-controlled monopolies.

Freedom of action through technical rather than territorial escape is the alternative option available to developing country manufacturers. The industrialized world is highly competitive: be first with an imperfect product, rather than second with a better product. This in principle leaves space for alternative or improved technology from second line developers with differently-structured ambitions. Such developments may be wholly supported internally or are assisted by technology transfer from specialized businesses or institutions. "Technical escape" is a source of diversity, thus a counter-weight to monopolies. This possibility is, however, hampered by another evolution: the extension of patent scope and rights well beyond their initial purpose. Patents tend to be granted with broad claims, not all supported by disclosures, thus reducing the "technological space" left to second line developers. It would appear justified that, while patents become enforceable worldwide, their scope should be limited to the novel areas of technology verified by experimentation only and not be abusively extrapolated to cover areas unsubstantiated by experimental data: while patents should be respected, abuse of patent protection should not be tolerated. Broad access to new technologies through non-exclusive licensing should also be the rule when innovative projects are sponsored by public funding (another form of PPP). This is not always the case.

As a conclusion, all the evolutions that we can perceive point towards the extension of monopolies, resulting from the extension of IP rights, both qualitatively and geographically, and the assertion of market privileges. Restricted access in public health has an ethical dimension. Unified rules, however desirable, may have consequences requiring proper evaluation and measures, if they must be adhered to.

4.4 Discussion of technology transfer and intellectual property issues

Dr Julie Milstien commented on the difference between the concept of technology transfer in Mr Fournier's presentation and that described by Mr Daout of MVP, which was more a partnership with the transfer of a specific piece of know-how to a well-established developing country vaccine manufacturer. Dr Shaw said that the interesting approach described in the MVP model was not a *de novo* transfer of technology but moving a technology forward. Mr Daout replied that technology transfer depends on the partners to the transfer, and in the case of the partners involved in this model – the FDA and the Serum Institute of India, it is easier. In the case of a transfer from a large multinational company to the Serum Institute of India, there might have been more problems. Dr Widdus added that the distinction between transfer of a possible piece of a process and a proven technology is quite important. He noted the experience of CSL, which made a large investment to clean up their wholecell diphtheria and tetanus toxoids and pertussis vaccine as a basis for combination vaccines, and then Australia changed to acellular pertussis vaccine.

Professor Raw described an agreement his company had with Aventis. He noted that a developing manufacturer would not get technology if they did not have some basis in knowledge. His agreement was structured in a step-wise fashion (as described by Mr Fournier) as a way to improving ability with a view to being free of Aventis in the future, and this was a faster way of gaining the technology. The cost of the vaccine to the government is half of what it was when imported, so this allows higher access to the product. Dr Akira Homma described his company's experience of technology transfer for meningitis A and C polysaccharide vaccines in the mid-1970s with Institut Mérieux as not easy but a positive experience. Important points were sufficient capacity in the recipient laboratory to be self-sustaining in terms of the size of the market. He noted that many developing country manufacturers had disappeared, because even public sector manufacturers must show production competitive with the private sector. He added that the current meeting was very important for developing country producers to aid them on the IP issues for the next decade. Professor Raw added that now that developing country manufacturers are involved in R&D, joint development with multinational manufacturers could be the next step, with the possibility that one of the contributions from the developing country side could be the clinical trials implementation.

Mr Kaddar asked for further information from the presenters on good or bad experiences with technology transfer and what lessons were learned. He also asked whether there appeared to be an explicit strategy on the part of multinational manufacturers to outsource basic vaccines to the emerging suppliers and whether this situation is desirable and efficient. To the first question, Dr Petre replied that he thought that transfer was inevitable whether or not it was suitable. Dr Hans Kreeftenberg commented further on the difference between technology transfer as a turnkey project and joint development. Netherlands Vaccine Institute (NVI) is now involved in joint development with both BioFarma and the Serum Institute of India. The developing country partners will handle clinical trials, scale up and licensing. Because NVI wanted to be free to transfer technology to any reliable partner, they used the Robbins method which is in the public domain. The problem is in the purification process; since cross-flow filtration is patented they had to go to gel filtration. (See **Annex 5** for more details on lessons learned in the transfer of Hib conjugate vaccine technology by NVI.)

Regarding the second question, Ms Shanelle Hall observed that there was lots of activity in the vaccine market now, in UNICEF's view, and they were very optimistic, in comparison to the situation in 1998–99 when there was a market failure with vaccine shortages. UNICEF sees IFPMA manufacturers looking to enter the basic vaccine market and DCVMN suppliers developing combination vaccines. UNICEF prefers a balanced market. Dr Sadoff cautioned that we should not underestimate the technical difficulties of consistently producing millions of doses of combination vaccines, with the need to not change any production processes and the problem of interference between the components. It might be surer to go with a product that is proven to work than to wait for technology transfer. He also noted that he had commissioned an engineering firm to look at one of WHO's prequalified producers of hepatitis B vaccine. Although it was a good facility, it was not felt to meet US and European current good manufacturing practice (cGMP) standards, and wondered whether this was an issue.

In response to Dr Homma's concerns about the impact of compliance with the TRIPS agreement, Mr Garrison provided a clarification of the 2005 date of effectiveness of the TRIPS agreement. This is the latest date developed and developing countries (with the exception of least developed countries) must ensure that their patent legislation permits the grant of patents for pharmaceutical products, but Brazil and China have already introduced it, while India and Egypt have made use of the transitional provision. Another aspect of the 2005 impact is that countries making use of the transition period must keep a mailbox for patent applications, which will be opened and examined under the new regime. There may be relevant patents for India for example. Mr Caruso added that the only significant producing countries not adhering to the TRIPS regulation already were India and Egypt. There has been 10 years experience so far with pharmaceutical product protection and to date there has not been much impact. Dr Jadhav noted that they had not seen much impact since they had been predominantly interested in making older vaccines but that the situation may be different if they start to make newer vaccines.

5. Intellectual property and vaccine R&D

5.1 SAAVI approach to IP issues

Mr Daniel Eksteen presented the approach of the South African AIDS Vaccine Initiative, SAAVI. He started with a summary of the kind of IP issues encountered. The issues are diverse and relate to all aspects of the IP process. Many of these arose as a result of the fractal SAAVI business structure which, although it is a very progressive ground-breaking structure, presents interesting and complex business management issues. To name a few:

- There may be no information published prior to lodging for protection. In one instance, a query came back from a patent office with regard to claims; certain components of those claims were published in an article that pre-dates the lodging date.
- Scientists have claimed art, but when this is researched it is found that there is comparable prior art.
- Co-coordinating the input of scientists, lawyers, patent agents to all comply with time deadlines and queries has been taxing within the complex legal structure that SAAVI finds itself.
- It was found that a group that SAAVI are supporting financially (in terms of which SAAVI becomes the owner of IP) had a prior undisclosed contract with an international agency in terms of which they have given such agency control of the IP. This necessitated the following:
 - insisting on a comprehensive legal due diligence, by outside counsel, of all the groups who SAAVI support that have or can potentially create new IP;
 - renegotiating the agreement with the group;
 - supporting them in renegotiating their contract with the international agency (a process that is still ongoing);
 - coordinating the responsibilities of the offices of: the patent agent; the University Innovation Office; the Medical Research Council Legal Office; SAAVI; and the scientists – insofar as it relates to time deadlines, responsibilities and strategic decisions;
 - a meeting by all relevant parties, delineating an operational process flow and responsibilities of all. This included drafting lists of which scientists and Principal Investigators need to be copied for input on which patents or processes.

He then provided justification for the SAAVI approach. The SAAVI approach to IP would probably be one of centralizing control of IP in a decentralized fractal business structure. It was decided that this structure serves the SAAVI mission the best, and also gives the funders the assurance that the returns on the money invested are protected for the SAAVI cause, benefit the SAAVI cause, and do not inappropriately benefit outside parties.

5.2 IAVI IP policy

Dr Franz van den Boom described the International AIDS Vaccine Initiative (IAVI) approach. IAVI was created in 1996 to get HIV vaccines back on the public health agenda and facilitate removing the obstacles to develop preventive HIV/AIDS vaccines that were safe, effective and accessible for use throughout the world. Several collaborations have been set up, each of which has unique IP challenges. These include many country partnerships, with countries such as India, Kenya, South Africa and Uganda, and one in development in China. In addition IAVI is working with partners in Europe.

There is a common misconception that IP is not really an issue in the HIV field. Some of challenges to an IP policy implementation include: broad umbrella and vaccine component patents; stacking of royalties; negotiations typically starting at the private sector level of royalty rates and milestone payments; lack of IAVI ownership of IP to cross-license; countries now requiring transfer of technology to local manufacturers; US export laws preventing technology transfer, or even product transfer without licenses being in place. IAVI's IP policy works in a flexible manner, respects IP rights, analyses IP and obtains freedom to operate as required. IAVI will pursue reduction in trade barriers where appropriate. An analysis of possible instruments showed that owning the IP was the best alternative, whereas licensing IP rights gave much less control, and an access commitment was of minimal use. In order to respect IP rights, IAVI will comply with laws and regulations, keep information confidential, use proper documentation, including documentation of ideas that may lead to patents, routinely assess patents in the field, and pursue licenses when required. They will define trade barrier reductions and seek solutions that will not alienate commercial manufacturers to create solutions that will provide access in a temporal fashion – both to developing countries and industrialized countries.

5.3 Discussion on SAAVI and IAVI approaches

Dr Wecker, noting that some of the SAAVI collaborators own IP, asked whether this served as a lever to advance their mission. Dr Widdus added that neither organization explicitly talked about the IP created by their own investments, which should have considerable leverage around the access question. Mr Eksteen agreed that some SAAVI collaborators, such as Therion, owned components of IP which are added to those of SAAVI to produce a product, but he could not really say that in that relationship it served as a lever.

Dr Bale, referring to the issue of trade barriers raised by Dr van den Boom, asked what this meant: is public money tying their hands? And is this a new element in terms of vaccine development? Dr van den Boom replied that governments supporting IAVI have given unrestricted money. The trade barrier issue is the barrier to export material for clinical trials when all the licenses are not in place, and this is solvable in the early phases of research. He did not mean to imply that their hands were tied by the public sector.

Mr Kaddar asked for a description of changes to IAVI IP policy in recent years and why it happened. Dr van den Boom replied that IAVI's IP model has changed as IAVI has matured. They now wish to have more professional and outspoken policies on IP. In the early years they did not fully realize the complexity of the IP field. He asked if work on the access component alone was enough to assure access.

Dr Mahoney raised the question as to whether or not there is a fundamental difference between PPPs and private sector research of this type. He noted that it is documented that biotech firms make strategic judgments about whether they will seek a license or not for a patented technology, while, in contrast, the public sector must take a more conservative approach, in part because their activities are in a fishbowl, i.e. cannot achieve the same levels of secrecy and confidentiality. How does this difference impact IP management? Dr Widdus responded that, in the case of the PPPs, they are not so accustomed to dealing with commercial revenues but are interested in public health benefits, so there is an imbalance in their negotiations. Dr Sadoff disagreed. He said that his organization, AERAS, approaches IP exactly as it was done at his former company, Merck. They divide up the world with commercial partners on a commercial scale and argue about the emerging countries: that is the public versus the private markets. As a result of the negotiations, commercial partners need to show they have made efforts to provide the product. Thus, PPPs have to be transparent, but they have to have an IP strategy. Dr Widdus agreed on the need to manage deals in a professional fashion. But he felt the fundamental motivation was different, as PPPs run not for profit but for public health. Mr Caruso stated that Merck will not knowingly infringe a public patent. They need to deal with every piece of IP extant. If that makes Merck like a PPP, so be it. Dr Mahoney concluded the discussion by reflecting that many biotechnology firms make a strategic judgment on the necessity for a license, while this option may be less available to PPPs.

5.4 MVI experience with intellectual property issues

Ms Patricia Roberts presented the experience of the Malaria Vaccine Initiative (MVI), a global programme established through an initial grant from the Bill & Melinda Gates Foundation to the Program for Appropriate Technology in Health (PATH).

MVI's mission is to accelerate the development of promising malaria vaccines and ensure their availability and accessibility in the developing world. Malaria exacts an enormous public health and economic toll on developing countries. Existing interventions for malaria treatment and control—such as bednets, drugs and insecticides—are being used with some success. Tragically, even with these interventions, over a million children die every year of malaria. MVI believes that a vaccine is needed to have a dramatic and sustained impact on this devastating disease.

Malaria vaccine development faces unique challenges. Few pharmaceutical and biotechnology companies work in the field—largely because industry does not regard malaria vaccines as viable commercial products. Companies that are working on malaria vaccines do so almost entirely with public sector funding. With the virtual absence of malaria in high-income countries, companies cannot rely on an attractive market segment that will yield high prices. Moreover, a malaria vaccine is perceived to be technically complicated and this technical risk makes the field even less appealing.

Circumstances unique to malaria vaccines result in a complicated intellectual property environment. A successful malaria vaccine will likely combine multiple malaria antigens as well as more generic vaccine technologies (such as adjuvants), resulting in layered IP and a more expensive vaccine due to royalty stacking. The malaria-specific IP landscape is unusually challenging and limits freedom to operate in the field.

It is MVI's experience that the poor accessibility of malaria-specific IP poses an immediate and significant barrier to the development of a vaccine. It should be noted that these circumstances, and any appropriate responses to them, are specific to malaria and not necessarily applicable to vaccines with significant markets in the USA and Europe, nor to less technically complicated vaccines. That said, MVI recognizes that IP is necessary for innovation and is fiscally important to both biotech and the pharmaceutical industry.

MVI has discovered, for example, that vaccine developers are reluctant to work with the MSP-1 malaria antigen. MSP-1 is a leading antigen with good immunogenicity and animal model data, but the presence of multiple patents with overlapping claims reduces its attractiveness. Engaging in MSP-1 commercialization would require a lengthy and complicated technology transfer process. Researchers tend to favour antigens that are in the public domain or that are owned by a single organization.

Why does the IP landscape for MSP-1 not sort itself out through traditional channels such as technology transfer and the courts? Developers who want assurance of the rights to use MSP-1 would have to obtain licenses from no less than eight organizations. Though theoretically possible, a licensing transaction of this type would take years, require significant staff time, and cost hundreds of thousands of dollars in attorney fees. While companies routinely make such efforts on behalf of commercial products, the economics of malaria vaccines make developers more reluctant to invest in such cumbersome technology acquisition.

MVI is working with each of its partners to create an IP environment where the best science drives decision-making, unimpeded by IP constraints and other obstacles. Addressing the issue more comprehensively will help ensure the most meaningful impact on the vaccine development process. For this reason, MVI is undertaking a study to explore how best to implement a patent pool for malaria-specific IP.

Generic vaccine technologies have been developed by industry largely through private sector investment and on the basis of attractive markets. The malaria vaccine field can benefit from such technologies by increasing industry participation in malaria vaccine research and development. However, it is important to ensure that the public sector does not invest in these technologies only to have the company pull out of the malaria vaccine market or deny the public sector future access to the technology.

Adjuvants in particular appear to be important to the development of an effective malaria vaccine. While proprietary adjuvants are generally available at the preclinical stage, the public sector needs to carefully consider investment in a promising candidate using a particular adjuvant. The public sector should ensure that there is industry commitment to make the adjuvant available for clinical development and commercialization. MVI is currently exploring a commercial strategy for the use of adjuvants in malaria vaccine development.

5.5 Perspective from the NIH technology transfer office

Dr Rohrbaugh, Director of the NIH Office of Technology Transfer, characterized the mission of the NIH for global health research as important for political stability, economic development, humanitarian objectives, and globalization of health problems relevant to domestic health. NIH has an annual budget of US\$ 27.3 billion, mostly in extramural projects, which support basic research and development as well as domestic biodefence needs and global public health needs. NIH has a technology transfer programme, the primary aim of which is to benefit public health.

The NIH portfolio includes 2300 total pending and issued patents, 1500 active licenses, 250 active CRADAs, and about 200 products developed to date, of which 17 are vaccines and therapeutics. The success of their strategy is measured through case studies and reviews of public health impact. The Bayh-Dole legislation gives NIH fundees the right to patent products, and NIH has issued guidelines about how to do this while facilitating the availability of technology. NIH will not patent a product if (1) it is of low public health priority; (2) no further development is needed; or (3) patenting it would hinder access. The terms of the license permit research use, with a preference for non-exclusivity (83%), tailored to the appropriate fields of use. Recently NIH has required the development of markets outside of Europe and North America to meet public health needs. Dr Rohrbaugh described some of NIH's efforts in building infrastructure and policy, including workshops, and learning from developing countries and nongovernmental organizations about their needs. Early stage technologies have been transferred to public and private institutions in developing countries, with efforts to ensure that participating institutions have some level of R&D capability. Gaps have been noted in developing countries relative to IP management, laws and policies.

5.6 Discussion on MVI and NIH perspectives

Dr Friede asked for some specific implications of the MVI partnership with GSK: if GSK stopped development would MVI be in a position to continue since GSK has in-licensed technologies? Dr Roberts answered that in the case of GSK, although partners generally have obligations for technology transfer in the MVI agreements, they acknowledged that this would be difficult in some scenarios. She said the best solution is having a great partnership.

Mr Garrison asked for more details on the patent pool feasibility study. Dr Roberts explained that they were now engaged in the first stage of creating landscapes for the top 10 malaria antigens. Stage 2 will be to determine what sort of pooling strategies could evolve, given the landscapes.

NIH will file patents if deemed needed but not if they are deemed to hinder development. Mr Garrison asked how this determination was made. Dr Rohrbaugh responded that the basic question NIH asks is if the technology will be used and disseminated by commercial entities without a patent. If the answer is yes, then NIH looks to see if there is a need to patent the technology, especially if there is already a complex thicket of patents. They get an opinion on whether a patent held by the US Government could help or hinder the situation, compared to a private company.

Ms Hall asked whether PPPs are developing the demand side of the market. Dr Roberts described several activities: a market assessment, the recognition of the need for some information to give industry a credible predictable sense of demand. In addition, they are looking at several financing options. Dr van den Boom said that vaccine preparedness work for AIDS vaccines was going on in developing countries, in addition to modelling work, to have a clear idea of need and demand and their implications for financing mechanisms. There was an issue of timing for this type of work. Dr Wecker referred to GAVI's ADIP concept. There are two accelerated development and introduction plans (ADIPs), on rotavirus and pneumococcal conjugate vaccines, both of which have products in near-term availability, negotiate with manufacturers and deal with demand side issues such as disease burden. All this information is put into a package for advocacy for national governments, and to attract funding. Dr Widdus mentioned a meeting on this subject held by his organization, for which the proceedings are available.

6. Options and directions for action

6.1 Synthesis of day 1

6.1.1. Presentation by the rapporteur

Dr Milstien summarized the subjects for which formal presentations had been given the previous day and the key points of the discussion. She noted the following general areas of agreement: (a) among the benefits of IP are increased return on investment plus safe and effective products; (b) IP management is an issue; (c) IP issues are complex; but (d) most can be negotiated; and (e) acquisition of IP can help strengthen the leverage of negotiating parties. In terms of access, IP issues have to date not hampered access, although they could, and this needs to be avoided. IP can stimulate R&D, but to date has not been used to the extent it could have been, and it is not the only way to strengthen R&D. Several models for technology transfer had been presented, but it was important to note that the group was not working with a consistent definition of technology transfer. The emergence of strong developing country manufacturers raises new technology transfer issues. There was agreement that a major key to success for technology transfer was good partners, but it was noted that technology transfer could result in a shared monopoly.

Among the areas that need more discussion are: (a) how to deal with the complexities of IP, including patent thickets, patent pooling, training, increasing abilities to negotiate, and preparing in advance for projected future need such as biopreparedness; (b) ways to stimulate R&D in the face of lack of market, and the potential role of emerging suppliers in this area; and (c) considerations impacting access, including blocking of regulatory action by lack of IP (as provided for in TRIPS-plus FTAs), ways forward when IP cannot be negotiated, and the role of technology transfer, especially to emerging suppliers.

The role of WHO in addressing these needs would also benefit from further discussion.

6.1.2 Discussion on the Day 1 synthesis

Dr Tarantola noted that developing country manufacturers also apply for patents and reiterated the immense complexity of technology transfer.

Dr Petre, agreeing that there are several definitions of technology transfer, suggested use of the more restrictive definition: transfer of an existing technology to someone who wants to acquire it. The MVP case would thus not be technology transfer but joint development. Mr Daout suggested that the NIH definition of technology transfer, i.e. transferring know-how, should rather be used.

Ms Cecilia Oh stated that in UN agency discussions a generally broad definition, including not only technology but also know-how, has been used. This definition also assumes that the recipient can absorb the technology and innovate from that stage. Dr Tarantola then suggested that in the context of the meeting it should be recognized that there were several subcategories of technology transfer, each having different IP implications. Dr Petre added that it was important to recognize the broad range of activities included in technology transfer.

Ms Hall stated that it was difficult to define the pros and cons of technology transfer without defining its objectives. If the goal were to enhance access, that is different from a goal of economic development and national self-sufficiency. She noted that there were no data to show that prices of vaccine produced in developing countries were automatically lower than prices of vaccines produced in industrialized countries. For five of six basic EPI vaccines there are cases where developing country suppliers propose higher prices to UNICEF than do industrialized country manufacturers.

Professor Folb then read out a statement on issues that he felt needed more discussion (the complete statement can be found in **Annex 6**): (a) technology transfer is not a virtue in and of itself, but when it supports and serves, ideally, joint development; (b) there are important similarities between vaccines and pharmaceuticals developed for the “very neglected diseases” and each field has much to learn from the other; and (c) the role of WHO is critical.

Dr Bale said that IP was but one of the issues impacting access. The others have not been discussed, yet some of them require better specification. Tiered pricing has been an important phenomenon in the vaccine field. Markets are very important, and some countries have tried to create markets through other mechanisms, such as orphan incentives, which are preferable to research “prizes”. Dr Tarantola questioned the relationship between tiered pricing and technology transfer, and Dr Bale wondered if technology transfer might inhibit tiered pricing. He added that one had to be careful about inventing phrases like shared monopoly. In the field of AIDS drugs, tiered pricing may obscure the issues, and donations may be preferable. Dr Petre suggested co-exclusive monopoly rather than shared monopoly. Dr van den Boom added that the access agenda is much broader and more political, including regulatory structure, but it is beyond the scope of the meeting.

Professor Raw stated that part of the problem is sharing development around the world. He said that the North has no monopoly on innovation, but it is very difficult for developing countries to do basic research. They do not want to be colonized, and can contribute in the areas of production and clinical trials. Dr Bale, noting that Bangladesh is a member of IFPMA, said that it was in the interest of industry to have a global basis of research, and that to ensure survival of vaccine research in the longer term it would be essential to have partnerships with emerging suppliers and for R&D. He rejected the model of a North–South divide. Dr Petre agreed and added that the driving force is market control. IP has no value if there is no market.

Mr Caruso noted the impact of new patent laws on patent filings. Data from the Republic of Korea show that when product patent protection was introduced there was an exponential increase in patent filings from domestic companies, but not for multinationals. He predicted that the same trends will be seen in India. Dr Mahoney added that Korean patent filings in the USA showed the same slope.

Mr Richard Kjeldgaard gave a brief presentation showing how some of the assumptions made about IP can polarize discussions, using the example of evergreening. There is an assumption that there are significant and insignificant innovations and only significant ones should be patented. He gave the example of an antidepressant, paroxetine. The active ingredient was invented in 1977, a patent was granted on a specific salt form in 1988, and on another salt form in 1999. Three different companies received the patents. However, the 1988 innovation solved the stability problem, leading to the first product (Paxil, salt form A) being approved in the 1990s, and the second innovation allowed a liquid formulation and a price drop for the second product, which appeared in the USA in 2003. Thus it is difficult to judge trivial and significant innovations. Another assumption concerns overly broad patents, and he mentioned the case of DNA fragments and reach-through claims. He concluded that each situation must be analysed: patents do not function in isolation but in the context of anti-trust laws and the overall environment.

6.2 Options and directions to consider

6.2.1. Presentation by Christopher Garrison

This is a summary of some of the questions presented, following on from the opening presentation, to stimulate debate and provide a few options and directions to consider by way of background for the working groups.

6.2.1.1. Intellectual property and vaccines

What is the range of vaccine-related inventions that may now be patented (each new class of patentable invention representing a new opportunity to stimulate investment, or a new access bottleneck, depending on perspective)? In terms of the vaccines of most interest, what is the patent situation in the relevant countries (i.e. where produced, where used)? How will the geographical vaccine patent coverage likely change as the full effects of TRIPS are felt, over years or decades? For a vaccine producer, in which countries would it be most desirable to obtain patent protection? What is the extent of the know-how (including trade secrets) gap between developed and developing country vaccine manufacturers? Is it increasing or decreasing? What impact will the TRIPS protection of undisclosed test or other data have on vaccines in the future? What progress is being made on the issue of well-characterized products that may permit greater equivalency or comparability of vaccine products to be established?

6.2.1.2. Vaccine access and technology transfer

Could consideration be given to a systematic methodology for analysing issues of access to vaccines in terms of the various types of IP monopoly factor, e.g. a patent monopoly, a know-how (including trade secret) monopoly, an undisclosed test or other data monopoly and any other pertinent factors. Analysis could also look at the scope of those monopolies. Patent mapping (such as mentioned by MVI), patent license mapping and know-how mapping (as in the MVP example) might be undertaken where useful/justified. It might be interesting to characterize the gaps between the IP owner and any other relevant entities (such as potential competitors). Such an analysis will be dynamic, rather than static, as circumstances and capabilities change over time. Should these analyses be supported by case studies?

Imagine that a simple, idealized example of such an analysis revealed that an OECD vaccine manufacturer (selling a vaccine at a comparatively high price in both the developed and the developing world) and an emerging vaccine manufacturer are “separated” by know-how relating to one specific technical problem, and a product patent (in the relevant country/countries). What are some options for facilitating access to this vaccine (either in terms of the actual use of these options, or as a background to negotiation with the OECD manufacturer)?

- 1) The OECD manufacturer could adopt a tiered pricing scheme, which perhaps would have the merit of relying only on the manufacturer to put it in place. Schedule divergence and market segmentation may be future problems.
- 2) A procurement agency could negotiate a bulk purchase agreement with the OECD manufacturer, with a lowered (and hence more accessible) price likely to follow from an increased volume. More broadly, would procurement activities be affected by the increasing potential, post-TRIPS, for patent coverage in the home countries of potential competitors, in which case perhaps only the manufacturer owning the patent (or other IP) might be able to supply the particular product? What impact would this have for competitive tender processes?
- 3) The OECD manufacturer might grant a voluntary patent license to the emerging manufacturer (depending for example, on quality issues) accompanied by a transfer of the necessary know-how. There will be time scale issues with this option because the emerging manufacturer will need to obtain licensure of their own product. However, this has to be balanced against the longer term considerations. In general, there are significant business case considerations for private sector technology transfer and it is not clear what can be expected from this approach (e.g. packing and filling vs bulk production). There seems to be some difference of opinion as to the desirability of local production, for example, and the consequent impact on price.
- 4) The emerging manufacturer could apply for a compulsory patent license, along with entering into an agreement with a contract research company to develop and transfer to the emerging manufacturer the missing know-how. Again, the emerging manufacturer will have to obtain licensure of their own product and again this will have to be balanced against longer term considerations. The MVP has demonstrated an interesting possibility in terms at least of the know-how portion of the problem: how replicable can the MVP model be expected to be?

6.2.1.3. Vaccine R&D

What role does IP in developing countries play for OECD manufacturers as an incentive in terms of their vaccine R&D? How will a developing country IP system contribute to stimulating R&D for a health need shared with rich developed countries? How will a developing country IP system contribute to stimulating R&D for a health need *exclusive* to poor developing countries? It can be expected that IP plays little or no role in stimulating OECD-based private sector R&D for the exclusive needs of poor or non-existent markets – will there be little or no return on investment even if IP rights are secured? Additional incentives, or even alternatives, to IP must probably be deployed. What role does IP in developing countries play for private sector

emerging manufacturers based in those developing countries in terms of stimulating vaccine R&D? If and when they develop OECD equivalent technical capabilities, can they be expected to behave significantly differently from OECD manufacturers and focus R&D on the needs of rich markets, where the returns are greatest?

In terms of public sector vaccine research: following the Bayh-Dole Act, is the public sector taking on private sector characteristics (in terms, for example, of more aggressive, for-profit IP management)? What impact is this having on vaccine R&D pipelines? Where the public sector is funding research, what are the types of IP terms in funding agreements that best secure public health goals? What could be the impact on the “IP model” of vaccine R&D on the discussions and proposals for public sector vaccine development and production capabilities (the Institute of Medicine proposal)?

Public-private partnerships now bring tremendous hope and possibilities for vaccines to meet the needs of the developing world. What progress are the various vaccine PPPs making toward their goals? What have been found to be the most successful strategies for managing IP in PPPs? What are the best tactics to draw in the desired private or public sector partners, and what consequences does this have on the PPP IP model? How often can an IP agreement link a viable market to a non-viable market? What are the present expectations for future PPP success?

There is an increased potential for IP to act as a disincentive to hamper or block vaccine R&D. What is the effect of “upstream” patenting and/or patent “thickets” on vaccine R&D for the needs of the developing world? Is negotiation with and between different IP holders, where necessary, being successful or are vaccine R&D avenues being blocked? How could this phenomenon best be managed? Is patent pooling a possibility? Who best should take the initiative to create such a pool?

Overall, what role can the UN agencies, including WHO, best play: involved actor, catalyst, observer? How best to square the circle between profit-based (private sector) R&D and R&D based on the needs of the developing world?

6.2.2 Discussion on Garrison presentation of options

Dr Sadoff wondered what was the legal basis of countries prohibiting the import of vaccines. Professor Folb replied that it was quite simply through the regulatory process.

Ms Dipika Matthias gave a brief presentation on a platform technology for vaccine thermostability, on which PATH is working, with extremely complex IP issues. In exchange for public sector funding of key R&D efforts, the company has made some concessions to ensure price accessibility. A note on intellectual property and vaccine stabilization at PATH submitted by Ms Matthias is included in **Annex 7**.

6.3 Outcome of Working Groups

The final session, where reports of the working groups were presented and discussed, was chaired by Dr Charles Clift.

6.3.1 Report of Working Group 1

Working Group 1 chaired by Professor Folb, considered IP and end stage and currently underused vaccines. Dr Petre and Mr Alejandro Costa served as co-rapporteurs, and Mr Costa presented the report. The vaccines concerned included Hib and other glycoconjugates, DTaP, IPV, combinations based on DTwP or DTaP, MMR, rotavirus, HPV, etc.

To seed the discussion, the group was asked to address four questions. Their responses are included below:

1) *Are current IP issues limiting access to these vaccines?*

The group recognized that IP, understood as patent rights, had not significantly limited access to existing vaccines in the past. Many vaccines currently used were not covered by patents and more recently licensed vaccines are now off-patent. The case of recombinant hepatitis B vaccine has been cited by several contributors to the plenary sessions, to underline how ownership of rights to the dominating patents did not preclude the development of large off-patent manufacturing capacities, contributing to a substantial price reduction and broad access to this vaccine.

Patents are perceived as a potential future limitation to accessing new technical developments or improvements, including new combinations of existing off-patent antigens and new delivery devices, as a result of the upcoming universal TRIPS compliance. The case of the combination vaccine patent using aluminium phosphate, a well known and broadly used vaccine adjuvant, was cited by several participants as an illustration of possible abuse of patent coverage with the consequence of a limited access to such vaccines.

2) *Is lack of competition based on a limited number of suppliers and a limited transfer of know-how limiting access?*

The group identified examples, like glycoconjugates (Hib) and pentavalent vaccine (DTP–HepB–Hib) where IP, in the form of know-how rather than patents, has been a limiting factor to the diversification of supply sources. Different factors have also had an impact to limit access: lack of sufficient production capacity, itself resulting from insufficient market and demand analysis, or a broadening of the demand not considered in initial manufacturing plans.

The diversity of production sources including developing country manufacturers is perceived as an important factor in securing broad access to vaccines. Currently up to 70% of UNICEF supplies of EPI vaccines is assured by developing country vaccine manufacturers, who can play a crucial role to develop vaccines of particular relevance to developing countries (“neglected vaccines” include, for example, those against malaria,

schistosomiasis, leishmaniasis, trypanosomiasis), which are not listed in the portfolio of major international suppliers simply because the market would not provide a sufficient return on investment.

Access to technology by developing country manufacturers has been reviewed from different angles. IP is perceived as an instrument of monopoly, and the difficulty to organize negotiated access has been underlined by several participants. Successful negotiations require both partners to be equally “potent” to develop win-win situations. This appears as a serious limitations to small manufacturers having little to offer in the face of major producers. An emerging evolution is the development of IP in developing countries. An important consequence of TRIPS compliance will be to secure freedom of action by technology outside the scope of existing patents. The management of IP and particularly patents has been mentioned by several manufacturers as a major difficulty: cost of preparing and filing patent applications, cost of assessment of the patent environment of a specific project (patent mapping), duration and cost of litigation. All these aspects place small manufacturers at odds to develop their own technology and have the result that patents are a powerful instrument of monopoly reserved to the large international suppliers of vaccines.

3) *Could technology transfer arrangements play a constructive role?*

Several PPPs have been set up in recent years and appear as a promising model. Key success factors were identified: commitment, trust between the partners and clear medical and market need. The MVP was presented to the meeting and referred to by several contributors as a model for development of technology in developing countries. While it is clear that MVP cannot pretend to be a universal model, its structure is of particular relevance and possibly the only practical approach for the “neglected vaccines” already mentioned. Critical success factors identified for MVP were: funding, flexibility to meet market needs (especially pricing policy), objective of profitability and leadership. Another example of a successful technology transfer of an “underused vaccine” component was the transfer of Hib conjugate vaccine technology, as described in **Annex 5**. Although there are many similarities between the MVP and Hib projects, there are also specific differences between technology transfer of neglected vaccines and underused vaccines. Leadership under the umbrella of WHO and other international organizations appears as a critical success factor to all projects supported by the Gates Foundation.

4) *What could be the role of WHO and other international partners in each of these situations?*

WHO could play a leadership role in negotiations, sensitization to public interest, and to safeguard public access. In the face of the growing importance of such limitations in the context of TRIPS, the group proposed to create a common “patent service pool”, accessible to DCVMN members to help them out through patent-related questions they may have in relation with their own projects. The role of this resource must be limited to advisory functions. It is understood that WHO and other international organizations cannot be themselves a negotiating or intervening party.

6.3.2 Discussion of the Working Group 1 report

Mr Caruso reacted to the idea of a patent evaluation resource for developing country manufacturers. He said there should be sensitivity to anti-trust concerns for a group action like this. Dr Petre said that the Working Group recognized this, but hoped there could be an international resource, limited to an advisory function. Mr Kaddar asked whether WIPO and WTO provide advice to Member States in this area, what specifically could be the role of WHO, and whether doing case studies on one or two PPPs would be useful. Mr Kjeldgaard said that WIPO gives advice, but he was not sure that they could respond to all the needs enumerated. WIPO does give advice to Member States on TRIPS and the August 2003 agreement, but not to companies and other nongovernmental entities, and WIPO and WTO have an agreement for this purpose. Member States also ask for assistance in understanding IP policy, such as legal policy on the impact of Bayh-Dole-type legislation on publicly funded research. Ms Xiaoping Wu said that WTO has less freedom to give advice to Member States. Rather, the Secretariat prepares compilations of views raised by Member States during negotiations.

Dr Clift observed that public interest IP advisers might provide this type of advice. Mr Kjeldgaard gave an example of a request to Public Interest Intellectual Property Advisors (PIIPA) by the government of Peru to evaluate plant extracts. A patent attorney, speaking Spanish, gave some very specific advice. Some law firms can provide *pro bono* advice in some cases. Dr Clift suggested that Dr Widdus might be able to provide more information about PIIPA. Dr Widdus observed that mechanisms need to be discussed as to how to, first, improve people's basic understanding and, second, to give commercial advice. Mechanisms on how to do this need to be discussed. A statement that Dr Widdus presented in the context of the Working Group meeting is presented in **Annex 8**. In addition, he mentioned specifically the Center for Management of Intellectual Property in Health Research and Development (MIHR), on which Dr Mahoney provided more information. Dr Widdus also mentioned a meeting of donors to 17 portfolio-based PPPs with the PPPs themselves the previous week. The business model being used by these PPPs should be more widely adopted: working with business plans, in a commercial way, with a specific product and disease focus.

Dr Mahoney provided more information about MIHR. In the process of setting it up, they considered providing legal advice such as the DCVMN members requested, but decided not to because of liability insurance, which was impossible to obtain. They were informed by Lloyd's of London that it had stopped providing liability insurance in the case of IPR because the situation was changing so rapidly they could not calculate the odds. This situation has thus changed the dynamic of partnerships, so MIHR will provide information about achieving public sector benefit. Patent laws are local, so ultimately legal advice will have to come from local competency. But WHO could play a valuable role in this, as it does for drug and vaccine regulation by providing guidelines and minimum requirements. Dr Tarantola stated that the role of WHO and probably that of UNICEF would be limited to developing guidelines and setting standards. To be competitive, public and private manufacturers in developing countries have to source this expertise.

Dr Jadhav said that while he understood the perspective of international organizations, still IP is very complicated. They have identified certain specific issues, including developing a template document, access to unbiased legal review, filling out applications, and sponsoring a meeting for understanding implications post-2005. He said that for DCVMN to be able to continue to supply to UN agencies and to sustain the majority of UN vaccine supply, they needed assistance. Dr Janis Lazdins suggested reconsideration of the issues from the perspective of capacity building. The Special Programme for Research and Training in Tropical Diseases (TDR) has, for the past four to five years, been building capacity in the areas of GMP, GCP, and ethical reviews. He suggested that WHO consider capacity building from its organizational perspective in countries where it might be relevant.

6.3.3 Report of Working Group 2

Dr Sadoff, who chaired the group, gave the presentation. The rapporteur was Dr Friede. The products considered included malaria, HIV, TB, dengue, SARS, shigella, ETEC, flu, relevant adjuvants and delivery systems. Dr Sadoff stated that manufacture of these vaccines, when they exist, will cost US\$ 3–4 billion per year and save 5–6 million lives per year, thus it is serious business. The group considered the four questions below.

1) *Is R&D sufficient? Is the private sector sufficiently engaged in innovation for these vaccines? If not, in which cases can IP issues be used to stimulate R&D?*

The group felt the IP system is generally good, but in the absence of a market, the system is not able to promote R&D. Industry input in these cases is greater than expected but less than needed and mostly impacts on development and late-stage research. There are a number of patent thickets – too many IPs or no clear pathway, especially for antigen-adjuvant/delivery systems. A specific example of hepatitis C virus (HCV) was cited, where one IP holder was in such a dominant position that this inhibited concerted development by other groups, which might have led to the development of a vaccine. The group suggested several possible responses: mapping, which could be problematic if a full map were done, but just identification of key patents would be helpful, as would mapping of licenses and exploration of creative licensing technologies to provide a way through the thicket (on perhaps a geographical basis or factoring out the developing world market, leaving developed world markets for IP holders).

The R&D promotion aspect of IP is useful, and some universities and biotechnology firms have enlightened licensing policies (an example is NIH). More work and more advocacy is needed in this area. Licensors should have to demonstrate developing country implementation of licenses. Other approaches include more interaction with groups like the Association of University Technology Managers (AUTM), in the USA; the dissemination of best practices, including outlining a step-wise approach to IP management; interaction with university leaders to promote a strong educational role for public health policy; and establishment of an IP landscape.

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- 2) *Have the agreements entered into to date been adequate to assure access once a vaccine exists?*

The experience of partners is important, and they report that there is a perceived over-valuing of technology by some universities and small biotechnology firms. There is a need for education about how access to products for the developing world can be guaranteed. There are several possibilities that can be built into licensing agreements. When to determine pricing is an issue, as it is linked to major investment. It may be useful to disseminate best practices, and such policies as retracting technology if it is not used in developing countries, and to aim to give exclusive or co-exclusive licenses only where the question of developing country access is not relevant.

- 3) *Is the PPP model a useful one for vaccine development to achieve both goals: stimulation of R&D and enhancement of access?*

The PPP model is useful. Though PPPs are not completely proven, they have moved the field forward, because they give flexibility and the capacity to adopt a business model. However, they can be monopolistic and there is a potential for error; thus they need a broader and deeper field of vaccine candidates.

- 4) *What could be the role of international partners in each of these situations?*

International partners could play a useful role in the dissemination of enlightened IP policy, gathering evidence and developing IP landscapes. This may be a role for the IP Commission, especially to consider the role of developing countries in the process. They can also help with development of R&D capacity in developing countries, and to start preparing the world for the purchase of new vaccines to reduce the time gap between development and implementation.

6.3.4 Discussion of the report of Working Group 2

Dr Mahoney said that it was possible under various formulas to have an agreement on price at an early stage of negotiations by using cost-plus formulations, but one must use caution, as this is the most difficult and swampy area for public sector negotiations. Dr Sadoff suggested that one approach was to have an audit of costs by an independent group built into the negotiations. Dr Lazdins said that in TDR negotiations, price was addressed very early, and Dr Sadoff replied that he personally favoured the concept of licensing, because if governments and donors were not willing to finance product development, the funds must come out of the sale of the product, so the product developer needed to be able to access the proceeds. This work must be a continuous part of the development process, starting with evaluation of the market. Dr Tarantola mentioned other models, such as the ADIPs, where private money has been invested to promote the use of the product.

On the issue of PPPs, Dr Lazdins noted that PPPs by their nature do not look into the public health part of what is being delivered, that is, how to place a product within the health system. This is implementation research, on the value and effectiveness of this product, usually done as phase IV studies. This type of research is very expensive, but nobody is putting money into this. Dr Shaw stated that it is pretty clear in the USA and the EU that there is a mad scramble before implementation

to get disease burden data. WHO is looking at this for rotavirus. He wondered if the MVP is doing this as well, as it is the most powerful tool we can have. Dr Tarantola replied that WHO is looking after the surveillance aspect of the MVP, and there is a surveillance system already set up. Dr Widdus noted that although the PPPs focus on product development, most conceive their mission in terms of public health impact, so for some of them this kind of work goes right back to the design stage. They may, for example, evaluate delivery systems. IAVI has already begun stimulating discussions on demand estimates and policies on use.

Mr Caruso questioned the degree of detail that would be included in IP mapping. He said it was useful to do patent searches, which comprise the first step to assemble needed documents. For the next steps of understanding the claims and the critical step of defining the product under development and how it interacts with these IP claims, private legal advice is needed. He mentioned the internal IP mapping document that WHO had developed, and said there were some changes that should be made on some of the Merck products, which he would send to WHO. Ms Matthias added that in the vaccine stability area they are looking to legal counsel to see barriers to the path they are proposing to take. This analysis would be shared with partners, and so would be a benefit to the partnership. Dr Widdus noted that the issue of which patents that would be powerful and useful emerged only as the science became clear. Dr Sadoff said that a patent court in England threw out a key pertactin patent, which allowed a vaccine to be developed that otherwise could not have been – this was a classic example where IP was blocking access to a product. However, even today it is not proven how valuable pertactin is to the efficacy of acellular pertussis vaccine, thus showing that science is not the whole story.

7. Conclusion

Dr Clift then provided participants with a brief summary of the next steps: presenters were requested to provide a short summary of their presentations to Mr Kaddar by 27 April. The rapporteur would produce a record of the discussions, a draft of which would be circulated to all participants for comment. The presentation and the record would be placed on the Commission website in June 2004. He thanked the organizers for a valuable meeting.

Dr Tarantola added his thanks to all participants and to his colleagues, noting it was a complex meeting to organize but was a successful one.

Annex 1:

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Annex 2:

Agenda of the Meeting

Monday, 19 April 2004

- 09:30 Registration – coffee
- 10:00 Welcoming remarks & objectives Daniel Tarantola;
Miloud Kaddar
- 10:30 WHO commission on IPR,
innovation and public health Charles Clift
- 10:45 Review of previous WHO/IVB
documents, new developments and issues Christopher Garrison
- Discussion**
- (1) Experiences with intellectual property in the vaccine field**
- Intellectual property and access to vaccines**
- 11:30 Role of IP in the development and introduction of vaccines in developing countries Richard Mahoney
- (15 min) Discussion**
- 12:00 Additional IP parameters affecting access Martin Friede
(5-10 min) Intellectual property and Magnus Schoeman
avian influenza vaccines
- (5-10 min) Discussion**
- 12:30 MVP three-pillar approach to access, Marc LaForce
R&D and technology transfer
- (15 min) Discussion**
- 13:00 *Lunch break*
- Intellectual property, vaccine production and technology transfer**
- 14:00 Transfer of Technology: OECD Vaccine Industry Perspective Pierre Fournier
- (15 min) Discussion**
- 14:30 Perspective from the DCVMN Suresh Jadhav
(15 min) Discussion
- 15:00 Technology transfer issues Jean Petre
(15 min) Discussion
- 15:30 *Coffee break*

Monday, 19 April 2004 *continued.*

Intellectual property and vaccine R&D

16:00	SAAVI approach to IP issues (15 min) Discussion	Danie Eksteen
16:30	IAVI IP policy (15 min) Discussion	Franz Van Den Boom
17:00	MVI experience with intellectual property issues (15 min) Discussion	Patricia Roberts
17:30	Perspective from the NIH technology transfer office (15 min) Discussion	Mark Rohrbaugh
18:00	Adjourn	
18:15	Cocktails	

Tuesday, 20 April 2004

(2) Options and directions for action

09:00	Synthesis of day 1	Julie Milstien
09:15	Options and directions to consider	Christopher Garrison
09:45	General discussion	
10:30	<i>Coffee break</i>	
11:00	Working Groups	
12:30	<i>Lunch break</i>	
13:30	Working Groups Report Discussion Closing remarks	
16:30	Closure	

Annex 3:

Bibliographical resources on intellectual property and vaccine: selected references¹

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Annex 4:

Comments on intellectual property rights and vaccines for developing countries

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Issues related to IPR and vaccines in developing countries are of major importance and should be treated seriously and carefully. To do these issues justice requires greater preparation and more comprehensive collaboration with all stakeholders and partners. Unfortunately, the short time limit for comments on the background documents for the WHO Conference on Vaccines and IPR is reflective of a process that makes it difficult to achieve such objectives. Indeed, even on a first reading of the background paper on IPR and vaccines in developing countries it is evident that the beneficial role which IPR play in the development of and access to vaccines for both developed and developing countries is not given serious and careful consideration. It appears that the paper states fears about IPR and vaccines, not the facts. It would have been more constructive if the perspectives of experts who appreciate the positive aspects of IPR could have been incorporated in the background papers in order to provide a more thorough and balanced perspective. Also, the participation of certain key players in the area of vaccines and developing countries is missing. The central importance of GAVI as a model for public–private partnership, with its mandate to improve access to vaccines in developing countries, has not been reflected in the background paper. The absence of GAVI representatives from the WHO discussions regarding vaccines and developing countries is also unfortunate. These discussions would have benefited greatly from their input, knowledge and experience, and would have given more balance and rigour to them.

It would be useful to revisit some of the fundamental realities associated with IPR and vaccines for developing countries. These include the following points:

- Patents have been shown to facilitate the dissemination of information from inventors to the public – that is the nature of patents! While it is common knowledge that patents do not necessarily disclose all information a potential competitor might want in order to be able optimally to produce a vaccine (for example, confidential know-how is important for much vaccine production), it would be misleading to state that patents block the communication of information.
- Industry is fully aware that access to vaccines in developing countries is a serious problem. However, this inadequate access is not simply due to allegedly high prices. In many developing countries, vaccine coverage is still very poor for very low-priced vaccines (e.g. EPI vaccines). As a recent *Lancet* article points out, three million children will die every year because they are not reached with such basic vaccines. Intellectual property rights are also not the real barriers to access for needed vaccines in developing countries. Indeed, patents have not proven to impede competition between vaccine producers. For example, several global manufacturers rapidly developed hepatitis B vaccine, one of the earliest patented vaccines, despite the IPR on that product.

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- Experience has clearly shown that fundamental infrastructure deficiencies are the real barriers to access. Impediments to access in developing countries include a range of socioeconomic factors related to infrastructure (cold chain and other), long-term forecasting, finances, political choices, capacity building, and others.
 - There is a general consensus that intellectual property rights also do not pose a barrier to vaccine technology transfer, but rather serve as a means or mechanism to facilitate development and transfer of such technology. It should be noted, however, that the importance of technology transfer in relation to vaccines is often overstated. According to leading vaccine manufacturers, only about 15% of the cost of producing the vaccines is related to the bulk production of the vaccines. About 85% of the cost is associated with quality control, due to the biological nature of vaccines. It is very important to ensure that the biological materials used in vaccine production are rendered harmless so that they do not in fact cause the disease which they are designed to prevent. Due to the vital nature of quality control regarding vaccines, original manufacturers need to be very careful to whom they license their materials. Thus, technology transfer must be looked at on a case-by-case basis based on quality considerations.
 - An additional important point to keep in mind is that scientific hurdles remain the single largest barrier to the development of new vaccines. Even with major funding and research time, vaccines for many diseases still are elusive. The example of R&D on an HIV vaccine is illustrative of this situation, where very large amounts of resources over almost 20 years have been invested, yet a workable vaccine is still not available. Having said that, it should also be noted that there is a great deal of *research* going on in the vaccine field for a variety of diseases. The *development* of these vaccines, however, depends upon the funding available and the priorities set by researchers and funders alike. Thus, the issue of how to improve financing for the development of vaccines of particular importance for developing countries would be an important issue to explore further. Furthermore, as has been well-established, IPR play a vital role in the stimulation of and incentivization of R&D in vaccines and medicines.

Keeping these realities in mind, it would be useful to further explore how IPR are playing a constructive role in vaccine development and to examine prospects on how this constructive role can be expanded in the future. Furthermore, examining the role of IPR in giving incentives for innovators in developing countries themselves would help focus the debate on the particular needs of developing countries. The prospective role of innovators from developing countries doing R&D to meet their countries' needs should not be underestimated. Forward thinking companies in India, China and elsewhere are already using the incentives of IPR (or, in India's case, the prospect of stronger IPR in the near future) to start their own R&D in medicines. It could thus be useful to examine what lessons could be learned from such medicines research for stimulating vaccine research in developing countries themselves.

Annex 5:

Lessons learned in the transfer of Hib conjugate vaccine technology and the consequences for access to this vaccine in developing countries

J.G. Kreeftenberg, A. Hamidi, Netherlands Vaccine Institute

Introduction

The former National Institute of Public Health and the Environment (RIVM) in the Netherlands, now called the Netherlands Vaccine Institute, has a long history in the development and transfer of vaccine technology to vaccine manufacturers in developing and developed countries. In this respect, the transfer of fermentor-based DTP and BCG technology as well as the micro-carrier technology for IPV production have to be mentioned. In addition the institute has been active in the development and implementation of alternative methods for animal tests, to Reduce, Refine and Replace these tests in the production and quality control of vaccines. Usually the transfer of the respective technology took place in bilateral collaborations, as well as in the form of courses for the WHO Global Training Network, as well as the DCVM network.

Hib technology transfer project

In 2002, around 386 000 children under five¹ died because of *Haemophilus influenzae* type b disease, a disease which has almost disappeared in developed countries since introduction of Hib conjugate vaccines in their national immunization programmes (NIP).

Since 1997, WHO has recommended inclusion of Hib conjugate vaccine in the NIP, wherever resources are available and disease burden data show that this is a priority.

To address this problem and continue its role as a technology transfer centre in the future, the board of directors of RIVM decided to develop Hib conjugate vaccine and transfer the technology to developing countries. This resulted in a Hib project, which started early 1999.

The purpose of the project was to develop an up-scalable and patent-free production process for the large-scale production of Hib conjugate vaccine, using technology which could easily be transferred to developing countries.

To avoid unnecessary delays in licensing the product, it was decided to use existing technologies with a proven track record to produce a safe and effective vaccine, without violating existing patents and IP rights. For that reason it was decided to develop a PRP-T vaccine, based on the conjugation method originally described by John Robbins.

¹ IVB estimate

The second reason for choosing the Robbins technology was the fact that lot release criteria had already been established by WHO for PRP-T vaccines based on this technology.

Soon after the completion of the preliminary investigations, we started to talk with our first partner, Bio Farma, and discussed a project plan including all possible roadblocks and technical or regulatory complications we could anticipate. These included items like strain to be used, avoiding the use of media components of animal origin as much as possible, presentation form, regulatory aspects to be discussed with the Indonesian authorities, etc. We also discussed how to set up an effective email communication between our two teams, to manage the project and to avoid unnecessary delays. MS Project was used as a project-planning tool, to coordinate the various activities in Bio Farma and RIVM and to monitor the critical path. In addition we discussed how to ensure effective training programmes of Bio Farma technical staff in Bilthoven as well as in Bandung.

By mid-2001 we met the primary objective of the project and had established a pilot scale process, which was commercially viable and ready to be transferred to manufacturers in developing countries. At that time, we were faced with the policy of the Dutch government, to support only international organizations like WHO, WB and GAVI, but not bilateral collaborations, like the technology transfer of the Hib technology to developing countries.

Consequently, we had to decide to stop the project, or to try to find partners in developing countries, who were interested in Hib vaccine and willing to invest in the project. By the end of 2001 we had contracts until the end of 2003, with three partners, Bio Farma (Bandung), Serum Institute of India (Pune) and Biological E (Hyderabad). These contracts had, strictly speaking, no legal status, but were based on friendship and trust in each other's commitment and were in fact gentleman's agreements between the participating organizations. In these contracts the three partners agreed to give a financial contribution to cover the cost of the existing Hib infrastructure at RIVM, until the end of 2003. In addition it was agreed that if the project were to result in a licensed Hib conjugate vaccine and income for the partners out of sales of the product, RIVM would get royalties to maintain its technology transfer infrastructure for future projects.

In early 2002, partners were trained in Bilthoven in all aspects of the developed technology and started the necessary investments in facilities and equipment to produce Hib conjugate vaccine. In addition, all documentation on the process as well as the QC testing were shared.

In the meantime, RIVM continued to investigate the developed process with experimental production batches. The production process was divided into various steps, to allow a smooth operation with acceptable yields. In this respect, the storage conditions of the concentrated Hib culture supernatant, and purified PRP, were validated. An attractive purification of the conjugate vaccine, by cross-flow filtration, could not be used, because this technology was protected by a patent. Consequently a more complex gel-filtration had to be used. In addition, the storage conditions for concentrated Hib conjugate bulk were established, to allow a maximum

flexibility between conjugation and lyophilization steps. Products were characterized by immunological and biochemical methods and shown to meet WHO requirements for PRP-T. In addition stability studies were performed on experimental lots of Hib conjugate and consistency in manufacturing was demonstrated on experimental lots. Compatibility studies with DTP-HepB were also performed, to validate possible negative interactions between DTP-HepB and Hib conjugate after reconstitution.

For regulatory reasons, it was decided to produce the clinical lots as much as possible at the partner's sites. According to the draft WHO guidelines for pre-clinical investigations, a pre-clinical study should preferably be done on one of the clinical lots and results should be considered to reflect the safety of the process and not the site, where the process was performed. For that reason the pre-clinical study was performed in the Netherlands with the first clinical lot available and the results were shared with all three partners, to be used to license their product.

By the end of 2003, a phase I clinical study was completed successfully by Bio Farma and SII was ready to start a phase I clinical study by Q2 2004.

Although phase II clinical studies are still to be performed, at the time this report was written, it could be concluded that until now the technology transfer of Hib conjugate technology has been successful.

Lessons learned

Factors which had a positive impact on the project are:

- commitment of the top management to the project;
- friendly cooperation between project leaders and Hib teams;
- regular review of the project plan and monitoring of the critical path;
- clear objectives from the very beginning of the project;
- stable financial position of the project from the beginning of 2002;
- high motivation of the team members and project leaders.

Factors which had a negative impact on the project:

- uncertainty about the financial support for the project resulted in high staff turnover at the beginning of the project;
- organizations had competing priorities;
- a cross-flow patent on a generally used technology blocked the use of this method for the purification of the conjugate.

Questions raised at the meeting

To enhance access for vaccines of public health importance in developing countries, the following can be concluded from the Hib technology transfer experience.

1) *Are current IP issues limiting access to these vaccines?*

By following the conjugation method developed by John Robbins, we could circumvent conjugation patents, which protect Hib technology, used for the production of some of the existing Hib conjugate vaccines.

Due to a patent on the use of cross-flow filtration to separate conjugate from the free polysaccharide, we had to follow a more complex separation method such as gel-filtration. We did not try to negotiate with the patent owner, to get the rights to use cross-flow filtration, because we anticipated that this would have delayed the time to market and we did not have the budget and experience to start a legal dispute.

2) *Is lack of competition based on a limited number of suppliers and a limited transfer of know-how, limiting access?*

As concluded in the Mercer report to the GAVI Board, the limited number of suppliers of Hib conjugate combination vaccines resulted in a relatively high price of these vaccines and consequently limited access to these vaccines in developing countries. The report concludes that by creating a market for these vaccines, several emerging manufacturers, including our partners Serum Institute of India and Bio Farma, will enter this market in the near future. It is anticipated that an increase in vaccine supply and competition will lower the price of the vaccine and consequently increase the access to the vaccine in developing countries. It is our opinion that in addition to creating a market by GAVI, the other critical factor in access to the vaccine is to get access to the vaccine technology, which was the result of our Hib technology transfer project.

3) *Could technology transfer arrangements play a constructive role?*

Our experience with the Hib technology transfer project and the observations reported in the Mercer report to GAVI, have shown that technology transfer arrangements will result in an increased number of suppliers of Hib combination vaccines and consequently in more competition. This will ultimately lower the price and increase access to the Hib vaccine and its combinations.

When the MVP model is compared with the experience obtained in the Hib technology transfer project, there are similarities and discrepancies. As with the MVP model, the Hib technology transfer model is fundamentally a joint development in a collaboration between partners, who all have their own input and experience, critical for the project. It is not a turn-key project, based on copying an existing production process. The difference between the MVP and Hib technology transfer project is that in the Hib project, the technology transfer will result in increased competition and consequently in a reduced price and increased access to the vaccine in developing countries. In contrast, there is no competition for the meningitis A conjugate vaccine, because of the relatively low price of the product, as agreed upon in the MVP.

4) *What could be the role of international partners in each of these situations?*

First of all, it is important that international partners, like WHO, GAVI and UNICEF, are aware of the issues related to access to vaccine technology and consequently access to vaccines for developing countries, as described in this discussion paper. Without compromising their independent role in the vaccine world, they could approach governments and private donor organizations and explain that technology transfer of currently underused vaccines to manufacturers in developing countries is a critical process to ensure a sustainable and affordable supply of these critical vaccines to developing countries. Consequently they should support these activities, which are in line with the UN Millennium Development Goals.

Annex 6:

Submission by Dr Peter Folb

There are three themes that have received insufficient attention in the discussions so far, although passing reference has been made to them.

Firstly; technology transfer is not a virtue in and of itself. It is of benefit when it supports and serves development, especially when there is joint development. After all, industrial development, and research in general, translates to development of the country concerned, which in turn promotes wealth and progress. Conversely, technology transfer without the necessary collateral support and infrastructure can be a burden. We need to consider the necessary conditions for technology to serve research and progress, and we should give attention to those situations that make technology transfer more of a burden than a benefit to the receiving country or institution.

Secondly; speakers at this meeting have taken care to distinguish between the intellectual property and drug development issues pertaining to vaccines and non-vaccine medicines (pharmaceuticals), respectively. There are of course differences, but this is much less true when one considers the vaccines and pharmaceuticals developed for the “very neglected diseases” (the Type III diseases referred to in the 2001 report of the Commission on Macroeconomics and Health). The reason for my making this point is that there is much to learn from the experience in novel drug development of vaccines and pharmaceuticals for neglected diseases in both directions. Even at WHO there is experience in drug development for malaria, schistosomiasis and Human African Trypanosomiasis, for example, that would benefit the vaccine discovery and development initiatives that we have been considering (I refer here particularly to the work of TDR). Conversely, people concerned with novel drug development would have much to gain from what has been done in vaccine discovery (both conceptual and operational). I am thinking here, in particular, of the meningitis A initiative, the measles aerosol programme, and the training and development programmes encompassed in the Global Training Network (GTN).

Finally, this meeting needs to consider in more detail the role of WHO in technology transfer as far as it has bearing on vaccine discovery, field research and manufacture. I submit that WHO support is critical here, particularly as far as the most neglected diseases are concerned. The role of WHO is likely to include: (i) monitoring and measuring, and developing methodologies for achieving this; (ii) setting standards, such as WHO already does in its prequalification procedures and in defining minimum regulatory standards for vaccine evaluation; (iii) training, including through the Global Training Network; (iv) facilitating thinking that goes beyond entrenched and formal positions; and, (v) acknowledging the importance of country development, and ensuring that the conditions are met that make technology transfer an agent of true benefit and development.

I have seen examples where technology transfer, done with vision and altruism, has made substantial contribution to the development of countries. That is the approach that I hope in due course will be incorporated into our decisions and recommendations.

Annex 7:

Intellectual property and vaccine stabilization at PATH

Project overview

As its broadest objective, the Vaccine Stabilization project at PATH aims to facilitate overall development of a market for thermostable vaccines. This entails both supply side development – working closely with technology producers and vaccine manufacturers to develop and test thermostable vaccines with both price and product specifications required by users and buyers – and demand side development to help build the evidence and policy environment necessary to facilitate broad adoption of appropriate thermostable vaccines into developing country public health programmes. Thermostable vaccines hold the promise of improving the efficiency and effectiveness of developing country vaccine distribution by minimizing reliance on the cold chain and ensuring the potency of vaccines injected into children.

Key partner – Cambridge Biostability, Ltd

The landscape of stabilization technologies is fairly active, with a myriad of different formats and delivery mechanisms existing today, all at various stages of R&D. With the goal of minimizing disruption to public health programmes and overcoming the safety risks associated with reconstitution of lyophilized vaccine (i.e. a current method to extend stability, particularly for live viruses), the project has chosen the stable liquid vaccine format as its first line of pursuit. Cambridge Biostability, Ltd (CBL) is PATH's partner for the stable liquid format. This format broadly involves stabilizing the vaccine within sugar glasses (which requires spray drying the vaccine) and then suspending the particles in a non-aqueous solution for ready, liquid injection delivery. CBL holds many patents and trade secrets around both these processes. PATH's role has been to help advance CBL's technology by supporting and assisting with R&D involving vaccines of importance to the developing country public health sector. In exchange, CBL has committed to licensing their technology to developing country vaccine producers and minimizing their technology premium (in the form of upfront fees, royalties, etc.) in an effort to help contain the price of stabilized vaccine products for key public sector buyers.

Landscape outside of CBL patents

Since the intellectual property surrounding sugar glass stabilization (SGS) is complex and could potentially pose a barrier to commercial development of CBL's specific stable liquid format, PATH has commissioned a series of studies to better understand the patent families most relevant to the currently envisioned commercial products. Although most of the basic technological principles underlying SGS are in the public domain, the study identified 130 potentially relevant patent families, eight of which were considered highly relevant (as of January 2003). The study also found that most of the SGS patents were pending in developed countries (mainly in the USA and Europe), with developing country coverage fairly sparse. This bodes well for developing country manufacturers that might license the technology from CBL, as their freedom to practice risk may be minimized. However, a more detailed study of the intellectual property environment is underway (with results likely to be available by June 2004) to closely examine potentially relevant patents to a very narrowly defined set of commercial product specifications. If this study reveals potential freedom to practice risk in either developing or developed country markets (to the extent that developing country vaccine producers may also desire to enter developed country markets with a stabilized vaccine product), PATH may need to devise an intervention strategy. This could potentially include outright purchase of ownership rights if the patent holder is willing, acquiring licensing rights (including the possibility of patent pooling if many parties are involved), or altering its product development direction to avoid the risk of patent infringement. Whatever strategic direction is pursued, the aim would be to reduce both the freedom to practice risk and "technology premium" (resulting from multiple, stacked royalties) for developing country vaccine producers in order to encourage commercial development and availability of stabilized vaccines. It is of high interest to the Vaccine Stabilization team at PATH both to learn about IP mitigation strategies attempted by other vaccine development efforts and to consider and discuss the potential role for wider public sector involvement or other viable strategies to ensure accessibility of vaccines to the developing world.

Annex 8:

Intervention by Roy Widdus on Working Group 1 discussion

To serve the interest of public health in low-income, and middle-income countries, developing country vaccine manufacturers need better access to expert knowledge regarding intellectual property issues; in particular:

- to what extent and how intellectual property management rules will change after 2005;
- the intellectual property (including know-how) situation regarding specific vaccines.

WHO, the DCVM Network, WTO, WIPO, and other interested parties should consult with the new Public Interest Intellectual Property Advisors (PIIPA ; <http://www.piipa.org>) and the Center for Management of Intellectual Property in Health Research (MIPR) on ways to reduce the imbalance in access to expert knowledge in intellectual property issues.

As convening such a meeting with commercial groups may be difficult, IPPPH would be willing to do so with DCVMN.