WORKING PAPER

Patent issues related to influenza viruses and their genes

An overview

The Expert Report entitled "Patent issues related to influenza viruses and their genes" was commissioned by the World Health Organization from the World Intellectual Property Organization (WIPO) pursuant to WHA Resolution 60.28. As such, this Expert Report does not necessarily represent the views, opinions or stated policy of the World Health Organization.

The Expert Report constitutes the background paper to the Director-General's Report on "Patent issues related to influenza viruses and their genes" (Document A/PIP/IGM/3) which will be submitted to the Intergovernmental Meeting on Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits, to be held in Geneva from 20-23 November 2007. The report is undergoing expert review. An annex containing a "Patent Landscape for the H5 virus" will follow.

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Executive Summary

The World Health Assembly (WHA) has requested the WHO Director-General to commission an expert report on the patent issues related to influenza viruses and its genes in the context of a broad Resolution on pandemic influenza preparedness and the sharing of influenza viruses and access to vaccines and other benefits. (WHA 60.28)

The present paper reviews certain technical patent issues relating to influenza viruses and their genes, with a particular focus on the avian flu or H5N1 subtype. The paper does not directly address such questions as the role of patents in benefit-sharing, the impact of patents on virus surveillance arrangements and vaccine production and distribution, or the management of patents and other IP for the promotion of public health, instead it aims only to provide a neutral technical background for discussion of these broader public policy issues.

Overall approach

In seeking to provide technical information in the complex domain of intellectual property (IP) law, the paper is shaped by the following general approach:

- It sets the relevant patent issues in a practical context, while recognizing that policymakers need information about the principles that form the basis of the patent system and their practical application in the life sciences.

- It recognizes that the development, analysis and modification of systems to detect, monitor and respond to mutations in the influenza virus are at core public health matters that health policymakers must debate and resolve.

State of play

There has been a rapid, recent increase in patenting activity broadly referring to the H5N1 subtype of the influenza virus, in the context of vaccines especially but also relating to diagnosis and treatment. This activity emanates from a wide, and widening, array of players, in both the public and private sectors – established vaccine producers, new entrant firms, individual inventors, government agencies, public research and educational institutions, and researchers drawing on traditional medicine. The subject matter of these patents and patent applications covers recombinant gene sequences, other extracts and derivatives from the virus genome, new genetic constructs making

use of such material, diagnostics, and more general platform technologies for the production of vaccines and treatments that make use of genetic inputs from the virus.

The fact that much of the relevant patenting activity was initiated very recently means that it will be difficult, in the short term, to make definitive judgements about its impact on vaccine production and pandemic preparedness:

(i) patent applications typically take several years at least to be examined and for a decision taken on whether or not to grant a patent; in that time, the application may be withdrawn or rejected, or the scope of its claims narrowed.

(ii) an international ('PCT') patent application only translates into patents with direct effect under national law if and when the applicant chooses to seek protection in a specific country, so the existence of a PCT application does not imply that protection will be actively sought in all PCT countries.

Relatively few patents or patent applications claim bare H5N1 genetic material as such, although some cases exist and may require closer examination, since they could constrain wider downstream usage of the genetic material claimed, such as in the development of new vaccines or production of vaccines. Many more patents or patent applications cover specific uses of the material in the context of diagnosis, vaccines or treatment, and could not legitimately be used to constrain parallel development of alternative uses of the same genetic inputs.

This general patenting trend represents a considerable investment of resources – both private and public – in the search for an effective response to the public health threats posed by the influenza virus, and of the H5N1 subtype in particular. This patenting activity signals an intensive, broad based and diverse practical response to a potential health crisis, a development that may in principle be welcome. Even so, this same level of activity has given rise to concerns that key technologies and their fruits – diagnostics, vaccines and treatments – may not be accessible equitably, including in the light of genetic material. Without accessible analysis of the emerging patent landscape, the sheer complexity of the evolving patent coverage of H5N1-related technology may create obstacles in itself for those seeking to clarify their freedom to operate in vaccine development and production.

Yet many existing vaccine production methods and other technologies now widely used for vaccine development are not covered by patents. Those that are patented in some countries are not patented in many others where they are therefore free to be used. The bulk of the most recent patenting activity – predictably enough, since it is by definition new technology – covers emerging

technologies that are as yet unproven for mainstream production (and are not approved by regulators), but may be of benefit in the future.

A note on terms used:

Terms such as 'virus' and 'gene' have diverse application and shades of meaning. Some distinctions have significant implications: for instance, the difference between 'virus' referring to a physical entity and 'virus' referring to a type or subtype (e.g. 'the H5N1 virus', referring to a subtype of 'the' influenza virus). There may be legal implications arising from these different shades of meaning, such as the difference between property rights in a certain virus specimen as physical material, and rights over an isolated gene claimed as an intangible invention. For the purpose of this paper, the following terms are used:

Specimen: the physical tissue taken from a human or animal subject which may contain viruses of interest, present within infected cells included in the specimen.[1]

Virus: either a specific virus such as is present in an infected cell (potentially prior to its specific identification and the determination of its subtype), or a reference to the influenza virus collectively as a general type of virus.

A glossary of terms is provided below.

[1] See, e.g. WHO guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection, 2005

1. INTRODUCTION: KEY PRACTICAL POINTS

This paper provides technical information on patent issues related to the influenza virus and its genes. It aims to do this within a broad policy framework and with some detailed description of patent law and policy, as the issues raised are inherently complex and technical. But it also seeks to address core patent issues of immediate concern to the international public health policy community, as expressed in recent debates, in an accessible, practical manner. As noted, it does not directly address broader questions relating to virus sharing, benefit sharing and IP management strategies for public health, but aims to provide a factual basis for discussion of such issues.

The following points aim to give the discussion of patent law a practical orientation:

(a) Illuminating the landscape

(i) Many live patent applications and patents cover derivatives or uses of genetic material from the influenza virus. This activity has increased sharply for the H5N1 subtype in recent years. This rate of activity means that patents are a direct practical issue and need to be taken into account in reviewing options for the development, production and dissemination of flu vaccines and treatments.

(ii) Enhanced use of patent information, and the development of comprehensive and accessible patent landscapes, would help identify what is being patented, by whom, where, and with what effective legal scope; in turn, this would shed light on the overall impact of patenting activity as well as emerging trends in flu-related research and development.

(iii) Not all relevant patents are in force in every country; in fact, most are likely to be applied for and enter into force in only a minority of countries (those countries are likely to be the most significant in terms of production capacity and economic development status in general). When different national patent offices examine patent applications for the same invention, they may grant patents whose claims have considerably different scope. Therefore what is patented in one country may be in the public domain, and free for anyone to use, in another country. Clarity about the effective legal scope of claims, and about the geographical limits of relevant patents, will be a key practical question in pandemic planning, and in considering how to extend and update vaccine production capacities.

Not all patent applications translate into patents at all, either being rejected by the patent office, or being withdrawn or lapsing while still pending applications. Claims are often amended and narrowed in the course of examination and prior to the grant of enforceable patent rights.

(iv) Increasingly many patent applications refer directly to genetic material from the H5N1 subtype of the flu virus, to derivatives or constructs from viral genetic material, such as virus-like particles or peptide antigens, and to derived information such as sequences obtained from databanks. Just because a patent refers to such a material, or a disclosed invention uses such material, does not necessarily mean that the material is claimed as an invention nor that it falls within the exclusive legal scope of the patent.

(v) Patent documentation can provide early insights into how specific virus specimens are used in research and vaccine development, and emerging trends in research and development on the influenza virus, including the evolving technological and economic framework for vaccine development. Patent applications are generally published 18 months after the first filing date, generally well before a new medical technology can move close to commercialization.

(b) Clarifying patent law principles and issues

(i) What is patentable?

'Patentability' refers to the criteria that apply when assessing whether a claimed invention merits protection by a patent. Just because an invention is patentable in principle doesn't mean it will actually be patented – the originator of the invention has to undertake a series of concrete steps actively to pursue patent protection in each country or region.

Actual decisions on whether a specific invention is patentable are taken in the framework of national or regional patent laws. These laws are in turn shaped by general international standards, but apply those standards in different ways, making use of flexibilities built into the international legal framework.

A full understanding of the potential impact of patents in relation to the influenza virus and its genes would entail a comparative analysis of how different patent authorities would deal with such questions as:

- Can patents be obtained on viruses as such?

- Can patents be obtained on genetic material extracted from virus specimens, or other material derived from such as synthetic virus-like particles, proteins and peptide antigens?

- What other forms of derivatives or applications of genetic material from the virus could be considered patentable?

- If a researcher does access a wild flu strain or its genetic content, what steps, inputs, or transformations are considered sufficiently inventive to produce a patentable contribution to technical knowhow? How has this assessment evolved over time, as the shared stock of background knowledge develops?

Some patent laws give explicit direction on such questions as whether and when an isolate of naturally occurring genetic material such as a virus should be patented. But actual outcomes also depend on how the general rules are interpreted and applied in practice, and assessments, for example, as to what kind of steps and insights would be considered non-obvious.

(ii) what is the nature of a patent right?

A patent is not a property right over physical material, such as a virus specimen. Rather, it is a limited right to determine whether, and how, others may use an invention, as a form of technological knowledge. For example, some national laws define the subject matter of a patent (an invention) as a technical solution to a technical problem. rather than a form of property right over physical material as such. In other words, ownership of a virus specimen may be independent of a patent on an invention derived from access to that specimen. On the other hand, the rights under a patent may limit how genetic material derived from a virus specimen is used or applied in practice, because this use may involve applying in practice the patented invention. For example, if a patent claims certain isolated gene sequence as a diagnostic tool, then the patent could constrain certain uses of that isolated gene sequence, even though the patent doesn't confer ownership over the virus specimen used in research.

The rights under a patent can be bought and sold, and transferred, like other property rights. They can also be licensed in many ways – exclusively, non-exclusively, in exchange for other technology (such as through cross-licensing or patent pooling), for various financial considerations, or free of cost to the licensee (e.g. humanitarian use licenses). Patents on the same invention can be owned by different

people in different countries, and can be licensed in different ways in different countries (the very same patented invention may be licensed exclusively in developed countries and non-exclusively or under humanitarian use licenses in developing countries).

The entitlement to apply for and to hold a patent stems from the actual inventor. Often it is the inventor's employer who applies for and holds a patent, at least initially (the patent may then be assigned or transferred to third parties). And both the ownership of a patent and licensed access to patented technology may be negotiated as a condition of access to other valuable material – ranging from direct financial payment for a research contract, to an agreement stemming from access to genetic materials. Practical IP management typically concerns the choice and exercise of such options over forms of licensing and structures of ownership of patents.

(iii) Linking patents with products

It is very rare for a single patent to correspond to a single vaccine or pharmaceutical treatment: there is usually no one-to-one correspondence between a finished product and a single patent. A vaccine or a pharmaceutical in a state that is ready for actual distribution to the public is typically a package or assembly of technology from different sources – including patented technologies, whether compounds or production processes, other ingredients such as adjuvants, drug delivery platforms, background knowhow and clinical trial data. In other words, ownership of or a license to the technology covered by a single patent is unlikely to give sufficient legal entitlement to all the necessary inputs to produce and distribute a vaccine or a treatment. This is why in practice there are considerable negotiations over various forms of licensing, cross-licensing, patent acquisition and transfer in order to put together viable technology 'packages'.

(iv) What is the scope of patent rights on inventions related to viruses or genes?

Patents on upstream technology such as research tools may create rights that reach through to the practical application of technologies, such as vaccine production. A patent on a genetic construct that has antigenic effect, for instance, may cover 'downstream' use of that genetic construct in producing a vaccine. And a patent on a method of producing a seed virus for vaccine production may extend to vaccines produced using that seed virus. But clarity on the actual

legal scope and geographical reach of such rights is part of finding , so as to explain freedom to operate issues.

(v) What exceptions may apply?

Exceptions and limitations to patent rights are recognized in international standards and are applied in many national laws to safeguard certainly public policy interests. For example, some national laws provide exceptions to patent rights allowing others to use patented technology so as to obtain necessary regulatory approvals, short of actual full-scale commercial production and stocking of a commercial inventory. This is normally done to ensure regulatory approval processes don't unduly delay entry of generic products on the market after the relevant patent expires. In some scenarios, pandemic preparedness may entail creating reserve capacity for vaccine production in the event of a pandemic, separate from routine commercial production of seasonal flu vaccines. Securing regulatory approval for subsequent use of patented technology may be one step in preparing such production capacity, prior to the step of actually producing inventories on a commercial scale.

2. PATENTS IN CONTEXT

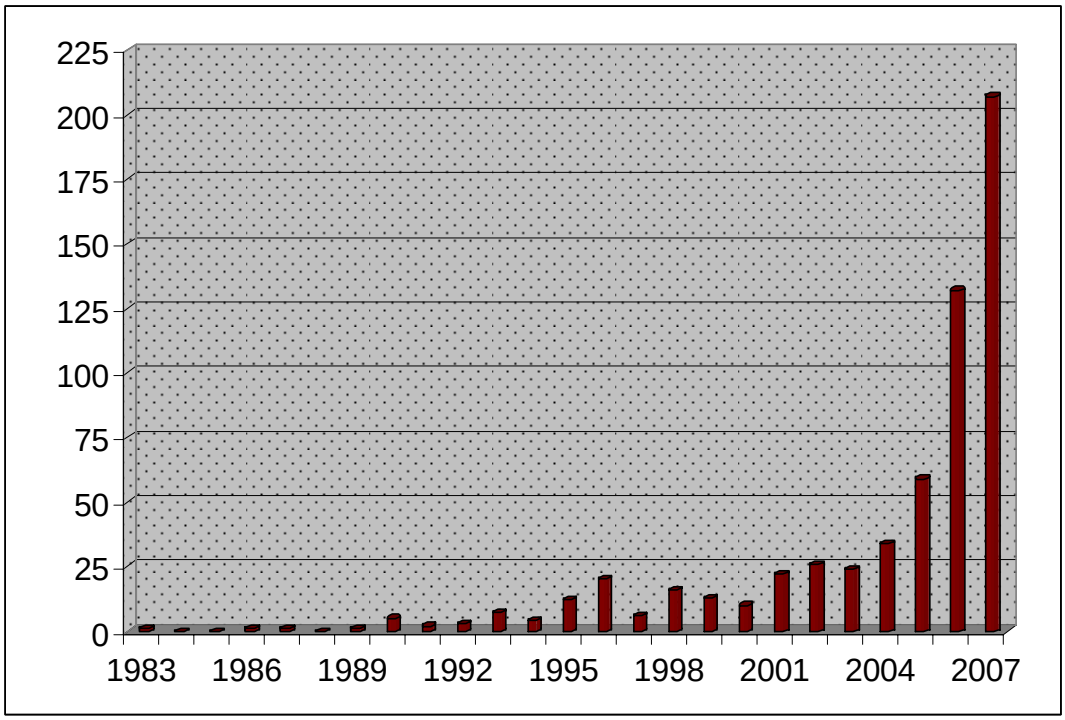
2.1 A snapshot of international patenting activity

Patents and the patent system are unquestionably of high significance in assessing both the nature of research and development relating to the flu virus, and the avian flu (H5N1) virus especially, and in charting pathways through this technological landscape towards effective access to and dissemination of needed technologies in the context of pandemic planning and general capacity building for vaccine production.

A very broad measure may illustrate how this is the case. The Patent Cooperation Treaty (PCT) is a mechanism for administering international applications that may mature into actual patents in some or all of the countries adhering to the PCT. International patent applications are generally published 18 months after the first patent document was filed disclosing a new invention. PCT publications do not give any direct indication of actual enforceable patent rights, but they do provide direct, early insights into emerging trends in research and development, and the identification of technologies that are considered to have commercial potential. It is also not a complete picture, as

many national and regional patent applications are filed outside the PCT system.

Looking at publications under the PCT therefore gives a rough indication of the trend in relevant patent activity, especially the activity with an international flavour (such as when an applicant especially wants to gain coverage in more than a small handful of countries and regions). The following chart gives an indication of all international (PCT) applications published that refer *in some way* to avian influenza or the H5N1 subtype (importantly, these do not necessarily claim viral genetic material even as partial subject matter of the patent; indeed, most do not). Nonetheless, the general trend is striking: of all relevant international applications since the first instance recorded in 1983, some 35% were published in the first 9 months of 2007. These publications therefore disclose relatively recent research and development activity, in the form of inventions that were first applied for between late 2005 and early 2006. There is considerable diversity in this activity, with publications from over 100 different actors representing a mix of private firms, individual inventors, public sector institutions and government agencies.



PCT publications referring to avian influenza or H5N1 virus;
publications up to 27.ix.07.

Observations: patent statistics

There is a striking acceleration of patenting activity that is broadly relevant to the H5N1 virus; 85% of all such PCT activity has been published since 2000, and almost 35% in 2007 alone (to date). This is a very crude measure of basic activity – it gives no guidance on the legal scope or geographic reach of eventual patent rights, and omits applications filed outside the PCT system. Yet even this crude measure epitomizes both the promise and the challenges of the patent system – it reveals much more applied research and investment of resources on this public health concern – but it points to a complex field of potential patent rights, difficult to analyse and to assess freedom to operate – in relation to development and marketing of products that use upstream technologies.

2.2 Some general patent law principles

No attempt is made systematically to review patent law in this paper. National legal standards and case-law are both complex and diverse. But the following general principles – common to many jurisdictions, and to some extent enshrined in international treaties – may provide useful background:

- Patents are in principle only available for technological advances that meet the legal definition of an 'invention' and that are new, not obvious and useful.[2] While the patenting of gene sequences or isolated genetic extracts has been controversial, many countries do provide for patents on isolated genetic material provided it meets the general standards for a genuinely patentable invention – for instance, an artificially isolated gene sequence that has inventive use as a research tool. In one early case, a patent was granted for the gene sequence used to express human insulin by novel means outside the human body, to produce synthetic insulin to treat diabetics. But the simple step of determining that a certain nucleotide sequence, genetic structure or genetic mechanism exists within a virus does not typically fall into what is considered a patentable invention.

- Naturally occurring substances, unaltered or untouched by human technological intervention, are not considered patentable. Hence a wild flu strain as such would be inherently unpatentable – put simply, it cannot be seen as an 'invention,' the fit subject matter of a patent. In

[2] The WTO TRIPS Agreement (art 27) provides – with very important optional exceptions that are discussed below – that "patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application." The terms "inventive step" and "capable of industrial application" may be deemed to be synonymous with the terms "non-obvious" and "useful" respectively.

general, patents are not available on bare genetic material as such: patents are only available for a true invention, although in many jurisdictions isolated or synthesized gene sequences have been considered patentable provided that they meet the general patentability criteria. For a patent to be legitimately granted, there has to be a degree of human intervention leading to an actual invention.

- A patent confers on its owner the right to exclude third parties from certain uses of the invention, as defined in the claims that are granted by a patent authority (rather than the claims as filed in the original application, which may be considerably narrowed or amended before being approved). There is no positive right to exercise the technology (which in the case of health technologies will typically need separate approval from the regulatory authorities). Under the competition law or patent law of some countries, it is considered an abuse of patent rights to assert a patent right with the intention of preventing use of technology that is not covered by the claims as granted.

- Patent rights only extend to the invention as claimed. Therefore, if a patented invention makes use of a certain gene sequence, but doesn't claim the gene sequences *as such* to be an invention, it can only be used to prevent the actual invention as claimed, not uses of that gene sequence in general. For example, if a patent claims a new vaccine structure that makes use of genetic material derived from wild flu strains, it could not be used to prevent others from using the original gene sequences or genetic materials in ways other than the specific structure that is claimed.

- Patent rights are territorial, and there is no international patent (the Patent Cooperation Treaty (PCT) is a system for administrative cooperation through international patent *applications*, which must mature into independent patent applications and potentially patents in national and regional jurisdictions to have any legal effect). Thus to obtain enforceable patent rights in a country one must actively seek a patent in that country's national system, or through an applicable regional system (such as that administered by the European Patent Office). The majority of patents are filed for in a relatively small number of countries, and most patents are not protected in the majority of developing countries, leaving the technology in principle free to use in those countries (unless of course there are constraints quite apart from that patent).

- Patents are typically filed at a very early stage in development of a biomedical product, prior to systematic assessment of the full viability of the technology. Patents in the medical field are typically published well before clinical trials are undertaken, and certainly long before

regulatory approval to dispense a new product to the market. A patent application in the public health domain is therefore typically published long before there is ultimate confirmation of the full clinical efficacy, suitability for production and distribution, and economic viability of the technology disclosed in the patent application. Equally, the publication of a patent application does not mean the invention as claimed is eligible for patent protection: many patent applications have to be amended and their claims revised or narrowed to be approved; many patent applications are refused or otherwise lapse before maturing into an enforceable patent.

- Each patent is the result of a specific choice actively to seek protection in the country concerned, and by no means are all theoretically patentable inventions actually protected. Moreover, while the grant of a patent on a claimed invention may carry with it a certain presumption of validity (this varies between countries), it is certainly no guarantee that the invention truly does conform with the patentability requirements, and a proportion of patents are found to be invalid as a result of subsequent broader scrutiny than is possible in regular patent processing, such as when a patent is enforced in court.

2.3 Core patentability questions

The very idea of a patent on genetic material, such as a patent claiming a gene sequence, has been the subject of policy debate and considerable controversy for a number of years, and in many countries. These debates have gone to the heart of patent policy and related public policy issues, and vigorous debate continues today. Yet there is a well-established practice of patenting genetic inventions in a number of countries, which may help shed light on those issues. The basic question that arises is: what genetic-based inventions are considered technically patentable, by reason of being new/novel, inventive/non-obvious and industrially applicable or useful?

2.3.1 Are patents granted on genetic material?

Genetic materials *per se* are not the direct subject of patent protection. The Convention on Biological Diversity defines 'genetic resources' as 'genetic material of actual or potential value' , and in turn defines 'genetic material,' as 'any material of plant, animal, microbial or other origin containing functional units of heredity.' Genetic resources are therefore essentially material, and are not intangible subject matter – the subject matter of patent protection is an 'invention' rather than a physical thing. One cannot obtain or assert patent rights over genetic material *as such*. As an analogy, an author

may hold copyright over the contents of book, but that does not give the author ownership over the book *as such*, which may be separately owned, bought and sold by others as a piece of physical property.

Accordingly, patents are granted over inventions *as such*, and they are not property rights over physical material that may embody an invention. Nonetheless, many patented inventions do include genetic material within their scope. An isolated gene may provide the mechanism for producing synthetic versions of therapeutic proteins. For instance, early in the history of modern biotechnology patents were granted on recombinant (cloned) forms of human growth hormone, of insulin and of other naturally occurring hormones such as relaxin. Many nucleotide (DNA) sequences have been claimed as patentable inventions, raising questions about when an isolated nucleotide sequence can be considered in itself to be an invention. This has led to extensive debate, for instance, about such questions as:

- how can a specified nucleotide sequence or an isolated gene sequence be considered 'new' when it exists in nature as part of the genome of a living cell?
- When can the act of identifying, isolating or transforming genetic material be considered truly inventive, and when is it a routine laboratory practice?
- What kind of use or function needs to be identified and disclosed for such genetic material to be considered 'useful' or having 'industrial applicability'?

Genetic resources are defined as 'containing functional units of heredity,' but they are not the same thing, conceptually or legally, as the functions contained within them. However, when employed in a novel, inventive and useful fashion, those functions may form part of a patentable invention – such as when genetic material is used in a new and inventive way to function as a research tool, or as a component of recombinant bacterium incorporating transgenic genetic material so as to express a therapeutic compound. If patents are granted on such inventions, patent law principles dictate that they should not cover genetic material as found in nature, and they should not amount to an assertion of ownership or control over naturally occurring genetic material. Some degree of human intervention is required to achieve a patentable invention, even if genetic inputs are involved. Such a patent, however, is not a form of ownership of the genetic inputs that contributed to or otherwise were used in the development of the claimed invention.

Two broad questions therefore arise in considering the interplay between patents and genetic inputs to inventions:

- There may be a wide range of different rights, entitlements and obligations over genetic materials, such as physical property rights, custodial rights and obligations, and entitlements concerning prior informed consent and equitable benefit sharing. How do the entitlement to apply for and to hold a patent, and the rights granted under a patent, overlap or otherwise interact with these other rights over genetic materials used in the patented invention?

- When a patent claims genetic material – say, a particular nucleotide sequence – to what extent can this be considered patenting the genetic resource as such? What distinctions – legal, conceptual, technical – can be found between genetic materials as physical specimens, and legitimately patentable inventions? In other words, what level of human intervention and ingenuity does a researcher have to apply when working with a genetic resource to produce a genuine invention?

2.4 International standards, flexibility and national choices

Broad international legal standards establish in very general terms a common perspective as to what should be considered patentable. However, these standards are interpreted and applied in different ways in national and regional patent laws, and the various policy options and flexibilities available within the general international standards are exercised in diverse ways at the national level. This section attempts briefly to review the key patentability criteria as applied to inventions relating to the flu virus and its genes, in the light of various national choices taken within the international legal framework.

2.4.1 Inherent patentability

National patent laws differ considerably on what is considered fit subject matter for a patent. International standards exist, but leave open considerable latitude (or flexibility). The WTO TRIPS Agreement, while requiring in principle that patents "shall be available for any inventions, whether products or processes" provides for several exceptions that WTO members may apply in their patent laws:

- inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid

serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.[3]

- diagnostic, therapeutic and surgical methods for the treatment of humans or animals.

- plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes.[4]

WTO Members have latitude to apply these exceptions as they deem necessary under their national laws – for example, some patent laws specifically exclude surgical methods. These exclusions are significant to some patenting scenarios relevant to the flu virus. More specifically:

- Some forms of inventive procedures that make use of a flu virus might be considered diagnostic or therapeutic methods, and thus may fall into exceptions under some national laws (e.g. the use of a certain sequence in a new diagnostic method);

- Some otherwise legitimate inventions derived from or making use of a flu virus might be prevented from being exploited in order to protect ordre public or morality, including human life or health: thus under national law a patent might be refused on a flu virus engineered to be a more potent pathogen, because it would be considered contrary to ordre public, even if it were technically 'new' and 'inventive'.

Considerable discussion has centred on whether a virus, a synthetic virus like particle or a derivative gene sequence could be considered a 'microorganism', including in the context of interpreting this provision of TRIPS – this may be significant as there is an explicit obligation in TRIPS to include microorganisms as patentable subject matter. However, any such material would still need to pass the other tests for patentability – it is certainly not the case that any gene sequence, any virus, or any virus like particle could be considered legitimate inventions.

In some countries, the principle has been established that merely being biological in character does not preclude an invention from being patented. For example, in the UK, the patent regulations provide that an invention shall

[3] TRIPS art 27.2

[4] But plant varieties are to be protected "either by patents or by an effective sui generis system or by any combination thereof."

not be considered unpatentable solely on the grounds that it concerns "a product consisting of or containing biological material."[5]

On the other hand, there is an increasing practice at the level of national and regional patent law to provide for explicit exclusions for unaltered genetic materials; these exclusions are expressed in diverse formulations, reflecting the flexibilities perceived by lawmakers in the international standards. For instance, some exclusions under regional patent standards relate to

> "[a]ny living thing, either complete or partial, as found in nature, natural biological processes, and biological material, as existing in nature, or able to be separated, including the genome or germ plasm of any living thing"[6]
>
> 'the human body and the simple discovery of one of its elements, including a sequence or partial sequence of a gene'[7]

In some jurisdictions, certain forms of gene-related inventions are considered to be inherently unpatentable for moral reasons. For example, in European law the following are explicitly precluded from patent protection on moral grounds:

- human cloning
- modifying genetic identity of humans
- commercial exploitation of embryos
- modifying animals' genetic identity which causes them suffering and give no substantial medical benefit[8]

Observation: virus and genes as patentable subject matter

While this paper does not offer definitive legal assessments, it is likely in most national and regional patent laws that the naturally occurring flu virus, as such, would not be considered fit subject matter for patents, either because of the basic requirement in patent law to claim a true invention or because of specific legal exclusions of this subject matter. Bare genetic information or genetic isolates routinely extracted from a wild organism or flu virus are generally not considered patentable, because of the requirement that a patentable invention be novel and inventive, and because of the need for a sufficient utility to be disclosed for the invention as claimed. Merely observing that a certain gene sequence exists within a given organism does not add to humanity's sum of

[5] Schedule A2, paragraph 1, Patents Act 1977

[6] Andean Community Decision 486, art 15(b).

[7] Directive 98/44/EC of the European Parliament and of the Council on the Legal Protection of Biotechnological Inventions, (entered into force on 6 July 1998), art 5.1

[8] Directive 98/44 on the Legal Protection of Biotechnology Inventions, art 4

practically useful knowledge. On the other hand, certain genetic isolates and similar derivatives have been found in many cases to be genuine inventions under the law of a number of countries.

2.4.2 Novelty

To be eligible for a patent, an invention must be new or novel. Given that a patent is on an invention, an embodiment of a form of knowledge, this means that the technology must not have been publicly known before the filing of a patent application; in some countries, there is a grace period which means that if the inventor discloses the invention to the public before filing a patent application, there is still a limited time to file an application and still claim novelty.

The criterion of novelty has raised questions when an invention concerns or is derived from genetic material that exists in a natural context. How can an isolated extract of genetic material be considered 'new' when it is already present, in some form, in the human body?

This debate has long preceded modern gene technology: for example, a patent was obtained a century ago on the first isolated and purified adrenaline, a naturally occurring hormone, even though adrenaline is already present in the human body. When challenged[9], the court upheld the patent since adrenaline as it occurred in its natural state was of no value as a treatment for heart disease. What was 'new' about the patent was not the existence of adrenalin as such, but rather the knowledge about how to isolate and apply it as a new therapeutic mechanism.

The same would apply for the claimed novelty of genes or other extracts from naturally occurring genetic materials such as viruses. Even so, views and national practice differ on what forms of genetic information can be considered 'new' for patent purposes. In a practical context, initiatives have been taken to publish genetic information with the explicit purpose of ensuring that genetic information as such is clearly in the public domain and thus precluded from being patented: these include the Human Genome Project and the SNP Consortium.

Generally speaking, genetic information that is published without confidentiality constraints on access would be considered non-novel. This does not mean that the information must be available free of charge – genetic information available only on a paid-subscription database would still be

[9] Parke-Davis & Co. v. H. K. Mulford & Co., 189 F. 95, 103 (S.D.N.Y. 1911)

considered sufficiently public to preclude novelty and hence patentability – provided those accessing the data were not bound by confidentiality obligations regarding the data.

How a nucleotide sequence is published, and the relationship of the published information and the claimed invention, are also relevant for the determination of novelty. A simple fragment of a nucleotide sequence would likely be considered anticipated if it is simply part of a much longer sequence that was already published; to be considered novel it may need to be isolated along with some new useful quality that had not previously been disclosed. On the other hand, a polypeptide chain corresponding to a published gene sequence extracted from a flu virus may still be considered novel as it had not been disclosed in that form before (of course, it may be considered obvious to derive the polypeptide from the disclosed nucleotide sequence, depending on the technologies involved).

Observation: publication of gene sequences

The early, open publication of the gene sequence of a newly-isolated strain of the flu virus would directly preclude obtaining patent protection for the genes as published. And open publication would facilitate research and development on the broadest possible base. On the other hand, it would also mean a loss of leverage over downstream use of the sequence data, for instance in research on diagnostics, vaccines and treatments, since the sequence data would unambiguously reside in the public domain, free for all to use.

2.4.3 Inventive step/non-obviousness

Perhaps the most complex and debated of patentability criteria, the requirement that an invention be 'non-obvious' or involve an inventive step is nonetheless intuitive at a level of general principle: it should not be obvious or routine to someone working in the relevant field to undertake what is claimed as the invention. Yet interpreting and applying this principle in practice has led to considerable controversy and debate. The test has been the subject of considerable scrutiny by policymakers, and has frequently undergone review and recalibration by the courts.[10]

[10] Including most recently in the United States Supreme Court in KSR v. Teleflex, 550 U.S. ___, 127 S. Ct. 1727 (2007).

To be considered a patentable invention, a gene sequence needs to be more than technically novel, in the sense of not having been disclosed to the public before - it needs to be considered more than a routine or obvious step for a researcher to take. Thus considerable debate has turned on the question of when a gene sequence is considered to be inventive, when the sequence has been obtained through standard laboratory techniques, techniques that are now highly automated. Two general perspectives apply:

> On the one hand, the result should be unexpected, should somehow go beyond routine laboratory practice. Simply to direct a known sequencing technique to new subject matter, such as a newly discovered flu virus, could not be considered inventive.
>
> On the other hand, simply using routine laboratory techniques, such as gene sequencing, does not amount to a patentable invention; yet the mere fact that techniques are used in an invention should not *in itself* disqualify the claimed invention on the grounds that it is obvious, any more than using a screwdriver to build a new mechanism would be considered obvious – provided it is not the method itself that is being claimed as inventive, but rather the consequences of using the method.

According to one decision, "the philosophy behind the doctrine of obviousness is that the public should not be prevented from doing anything which was an obvious extension or workshop variation of what was known."[11] Equally, the doctrine is intended to ensure there is sufficient incentive for researchers to look beyond the bounds of routine research pathways.

In a biotechnology context, one authoritative review of the non-obviousness requirement expressed it as follows:

> "Whenever anything inventive is done for the first time it is the result of the addition of a new idea to the existing stock of knowledge. Sometimes, it is the idea of using established techniques to do something which no one had previously thought of doing. In that case the inventive idea will be doing the new thing. Sometimes it is finding a way of doing something which people had wanted to do but could not think how. The inventive idea would be the way of achieving the goal. In yet other cases, many people may have a general idea of how they might achieve a goal but not know how to solve a particular problem which stands in their way. If someone devises a way of solving the problem, his inventive step will be that solution, but not the goal itself or the general method of achieving it."[12]

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11 PLG Research v Ardon International [1999] FSR 116, 136.

12 Biogen Inc v Medeva plc [1997] RPC 1 34 (House of Lords)

Recent experience in European practice may be considered to shed light on the test of obviousness in relation to genetic sequencing in a public health context. For instance, a claim to recombinant DNA is obvious if the techniques used to produce the sequence were already well known. This has been found in the context of sequencing the hepatitis B virus (HBV): "… it would have readily occurred to the skilled person to try to complete the work [already disclosed] by identifying and characterising the primary structure of the DNA sequences encoding HbsAg and HbcAg within the said fragments of the genome of HBV subtype adyw and to express them in a recombinant DNA system such as, for example, that described in document (1) so as to produce antigenically active products. This would have involved nothing out of the ordinary for a skilled person in the field of molecular biology at that time as all the necessary methods and means (eg antisera specific for HbcAg and HbsAg) as well as techniques for the location and DNA sequence analysis were known in the art … The skilled person merely needed to proceed experimentally as done by previous authors … knowing from document (1) that the expression of antigenically active products was to some extent feasible in a recombinant DNA system."[13]

The bar of obviousness is also likely to be raised if there is already considerable background knowledge about the genome in question and the function of its specific genes. Given that the flu genome is the subject of intensive study and its functionality is widely published, this may be relevant to patents claiming genetic material derived from the flu virus. In another European case, this was a factor in denying the inventiveness of the isolation of a gene: "the existence of additional 7TM receptors was predicted in the prior art and the procedure for the identification of said additional member of 7TM receptor family has been well established. Consequently, the disclosure of the primary structure of an additional 7TM protein which is arrived at by following the well established methods disclosed in the prior art is not considered inventive …"[14]

The automation of gene sequencing techniques perhaps exemplifies this shift in understanding about what is a routine research activity obvious to the person skilled in the art. In other words, it is an example of how the changing technological background influences the determination of whether an invention can be considered obvious or inventive. The UK patent examination guidelines comment in detail on the lack of inventive step in such procedures:

> data mining to identify a polynucleotide or a polypeptide homologous to a polynucleotide or polypeptide, having a known function or activity, will not normally involve an inventive step. Moreover, while a specified degree of homology may serve to distinguish the newly identified sequence from one or more known, homologous sequences, it cannot

[13] Biogen Inc / Hepatitis B virus [1999] EPOR 361 (T 0886/91)

[14] ICOS Corporation / Seven transmembrane receptor OJEPO 2002, 293 (EP-B-0630405)

usually serve to establish an inventive step. It therefore follows that the identification of a human homologue of a previously characterised gene from another species is not inventive, and this is regardless of the methods used to identify the homologue. Whilst each case should be taken on its own merits, it is reasonable to presume initially that it is obvious to:

- identify previously unknown members of a known family by homology
- identify a gene in a database on known structural information about the corresponding protein
- assign a function to a gene by homology comparison with gene(s) of known function[15]

Generally, the search for homologues of known genes should be considered a regular research function, unlikely to be considered inventive in itself.

Moving beyond sequencing as such, a number of patents have covered the artificial mutations of gene sequences or other artificial genetic constructs, such as artificial virus like particles and new combinations of peptide antigens. The case law suggests that an artificial mutation of a gene may be considered non-obvious if it shows an unexpected advantage over the gene in its naturally occurring form, provided that advantage is common to all the claimed mutations, and is a specific feature of the mutated gene.

Observation: obviousness

Advances in gene technology, and the general state of the art, suggest that simply to sequence a gene using regular laboratory techniques is unlikely to be considered inventive or non-obvious. On the other hand, using standard sequencing techniques to produce an invention that is unexpected and runs contrary to established views would not make that invention obvious.

2.4.4 Utility

The requirement that a claimed invention be 'useful' or have 'industrial applicability' or 'utility' has been a particular focus in the debate over patents on genetic material. The debate has especially focused on concerns about speculative claiming, whereby gene sequences are claimed as inventions before any clear function had been determined, thus unfairly blocking the future

[15] Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the UK Patent Office (May 2005), para 32.

application of these sequences by researchers who may be able to identify beneficial functions. It was partly to deal with concerns about patenting gene sequences the United States Patent and Trademark Office (USPTO) issued Utility Examination Guidelines. This clarified that for an invention to be patentable, a general speculative reference to possible uses was not enough: there had to be disclosure of "specific, substantial, and credible" utility.

A major debate continues in many jurisdictions as to (i) what level of utility or specific application should be disclosed concerning a patented gene and (ii) whether the reach of claims should be limited to just the function disclosed, or any other function subsequently determined for that gene. National practice differs very considerably on these points and no particular conclusion can be drawn here. Options may range along a spectrum from allowing protection for any subsequent use of a genuinely new and inventive gene sequence, to restricting the scope of protection just to the exact function described in the patent, leaving other uses of the gene sequence free for others to employ.

One recent approach is found in the current revisions in train to the Swiss Patent Law, which would prescribe that protection under a patent on a nucleotide sequence derived from a gene sequence or a partial gene sequence existing in its natural state is limited to segments of the nucleotide sequence which give effect to the function specifically disclosed in the patent.[16]

Generally, there is an obligation on a patent applicant to disclose an invention that gives effect to a useful function, and is not a simple observation about a state of affairs in nature. Equally, the scope of protection of an invention – as defined in a patent's claims – is required to be limited to just that scope of material that achieves the intended results. Thus, if a claim is extended to hundreds of possible gene sequences, but only a few of them would actually carry out the claimed invention – for instance, in having a claimed antigenic effect – then the claim would be invalid inasmuch as it covered material that did not have the utility asserted for the invention. (See also the discussion of 'disclosure' in the following section).

Observation: utility or industrial applicability

National practices differ considerably but there is a trend towards denying patent protection for gene sequences as such, in the absence of any clearly disclosed and defined new function.

[16] Loi fédérale sur les brevets d'invention (Loi sur les brevets, LBI) Modification du 22 juin 2007, art 8(c)

2.4.5 Disclosure

A patent is in principle invalid if it does not fully disclose the invention sufficiently for a normally skilled person to put it into effect. This means, too, that claims to an invention cannot be speculative and can only be as broad as the invention disclosed in the patent document. So, for example, a patent could be invalid if it claimed a wide range of novel genetic constructs making use of genetic material from the flu virus, but did not explain how to create those constructs in a way that a technologist could produce all the scope of constructs claimed.

It is noteworthy, in practice, that many patent documents disclose the specific virus strains, or gene sequences derived from them, that were used in the development of the invention in question – see the observation below.

A current issue in international debate over patent law relating to genetic resources is whether there should be a distinct form of disclosure, tailored to deal with patents on inventions that make use of genetic resources. Differing views exist on the value and impact of such measures, which are present in the national patent laws of a number of countries. Such specific patent disclosure mechanisms may form part of the patent law, as an *erga omnes* requirement on all relevant patent applicants, or may be applied as a distinct contractual obligation, such as an obligation undertaken as a condition of access to specific genetic materials.

Further options in patent law include (i) imposing an obligation to disclose not merely the invention in general terms, but also the best mode known to the inventor of carrying out the invention in practice; and (ii) furnishing to the patent office all information known to be relevant to the patentability of the invention (such as publications that may be relevant to considering whether an isolated gene sequence is truly novel).

Observation: using disclosure for greater transparency

A review of existing patent applications demonstrates that a number of applicants already disclose the actual strains of viruses used in developing or implementing the claimed invention. Standard terminology for virus isolates and their gene sequences are used: e.g. A/Thailand/NK165/2005 (H5N1), A/shoveler/Egypt/03 (h5n2) or A/duck/Hong Kong/308/78 (H5N3). Existing search technologies allow identification of such patent applications on

publication, and monitoring of new applications well before they proceed to examination or grant.

2.4.6 Inventorship and entitlement to apply

The right to apply for a patent flows from the legitimate act of invention with the IPR going to the inventor. Parties other than the actual inventor can acquire the IPR, provided that there is a legal linkage, such as through an employment relationship, a specific contract, or the assignment or transfer of ownership. The IPR may therefore be transferred by contract: for example, it is possible to require ownership, part-ownership or other interests in a patent on downstream research as a condition of access to a specific material

Ownership of a patent, such as a patent on a gene-based invention derived from genetic material, should be distinguished from ownership of the genetic material itself. For instance, no ownership of a patent could in itself lead to the transfer of ownership over a physical specimen containing a virus. A physical specimen can be transferred to a researcher, who then uses the specimen to develop a patented invention, with the provider retaining ownership over the specimen as such: this is not unusual in current research practice. Moreover, ownership of physical specimens, and the rights of access conferred by such property rights, can be used in practice to leverage access to patented downstream technologies – although the benefits of such an approach need to be weighed against any deterrents or unintended obstacles to desired research and development.

This paper does not discuss the possible approach taken to management of virus surveillance mechanisms, and structures for ensuring appropriate benefit sharing in the development and dissemination of flu vaccines. Nonetheless, it should be noted that there is a wide range of options for structuring ownership, exercising, licensing and otherwise managing relevant patents, and this diversity of options may need to be considered by policymakers in the review and further development of these mechanisms.

Observation: inventorship, ownership and entitlement to apply

If two research teams within a research partnership contribute inventively to the one patentable, and one team seeks a patent without recognition of the other, then various legal remedies are available. While the entitlement to apply for and to hold a patent must be derived from the genuine inventor(s), ownership of patents can also be transferred on the basis of contracts relating

to non-inventive inputs to the invention – such as research contracts for paid research, or material transfer agreements providing genetic materials.

2.5 Patents and the vaccine development pipeline

One way of framing relevant patenting trends and related patent issues is to review the vaccine development pipeline, as distinct issues linked to the flu virus may arise at each stage of development, production and distribution of vaccines.

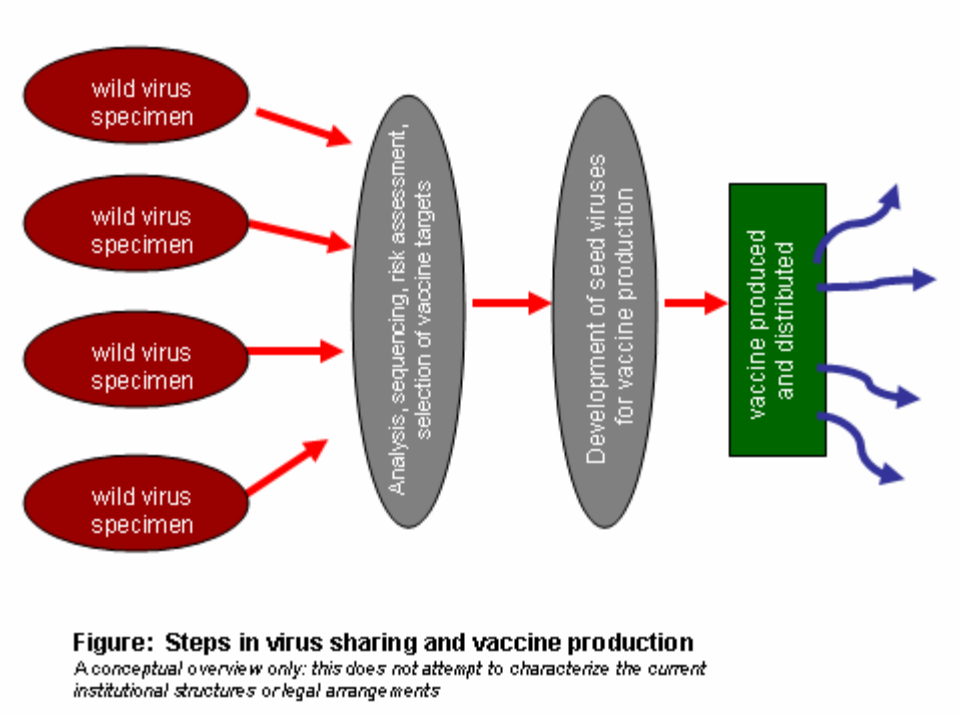


Figure: Steps in virus sharing and vaccine production
A conceptual overview only: this does not attempt to characterize the current institutional structures or legal arrangements

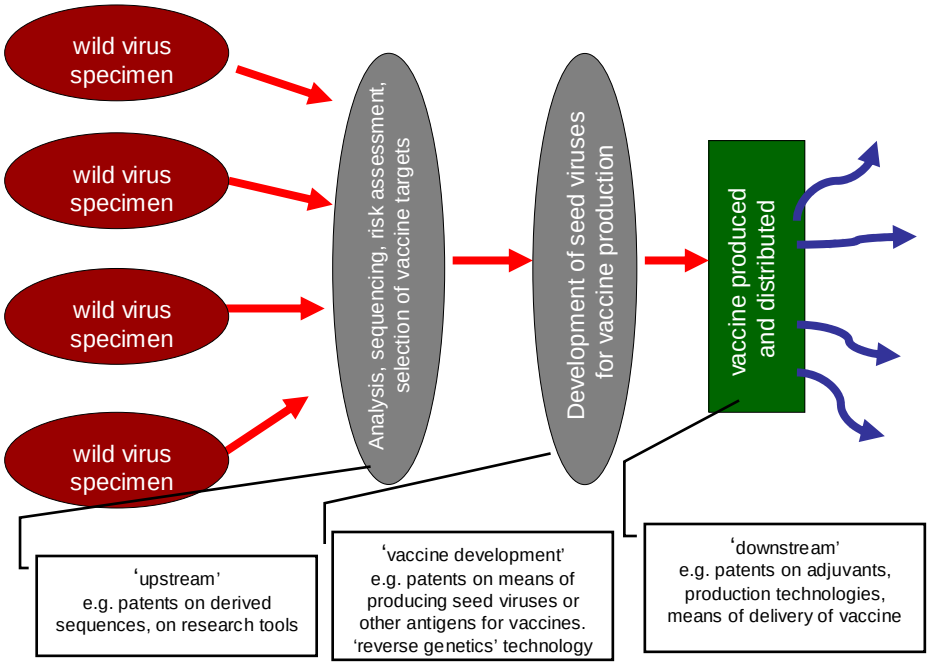
2.5.1 Patenting activity along the vaccine development pipeline

The key steps in the isolation, characterization and downstream use of the virus and its genetic material include:

- Flu specimens are collected from humans or animals
- The wild flu strain is isolated, characterized and sequenced, and its risk assessed.

- Flu strains are selected for vaccine production
- Viruses are transformed, through certain technological processes, into a form suitable for vaccine production – 'the seed virus.'
- The seed virus is provided to vaccine manufacturers
- Vaccines are produced by established or new (potentially patented) technologies
- Distribution of the vaccine doses

Intellectual property issues and practical intellectual property management questions may arise at each of these stages, and may have bearing over the way in which the patent system delivers socially beneficial outcomes. Some may have little to do immediately with the patent system but may nonetheless have considerable bearing on patent outcomes. For example, when the genetic sequence of a new virus strain is determined, if it is then made publicly available it would immediately be considered not 'novel' for purposes of patent procedures from the day it was published (taking into account 'grace periods' in some national laws).



In reviewing the patents that may be considered relevant overall to the flu vaccine, the development of vaccines, preparations for a global response to a flu pandemic, and benefit-sharing issues, it may be helpful to bear in mind the sets of patents at the various stages along this pipeline. As the above diagram suggests, these can be grouped very roughly as 'upstream', 'vaccine development' and 'downstream', although these categories should be used with great caution as an overall guide only.

'Upstream' patents may include patents on gene sequences or other derivatives such as peptide antigens derived from the virus, and research tools that are used in the isolation, identification and sequencing of viral material obtained from specimens.

'Vaccine development' patents may include patents on the techniques used to create a vaccine, such as the seed viruses prepared for the production of seasonal flu vaccines. The 'reverse genetics' patent family is often discussed as highly relevant to production of seed viruses for vaccine production.

'Downstream' patents may include patents on general vaccine production technologies that may be relatively 'neutral' to the exact genetic make-up of the specific viruses the vaccines are produced for, but would nonetheless 'use' genetic material derived from a virus to produce a specific vaccine against that virus. They may also use technologies that are technically unrelated to access to and use of the flu virus as such, but may be vitally important in an effective response . One widely discussed example are patented adjuvants, which by stimulating a stronger immune response from a given dose of vaccine would greatly increase the number of available effective doses from the volume of vaccines produced, thus inoculating many more people from the same level of production.

Observation:a product as a technology package

It is most unlikely for an actual vaccine, or pharmaceutical treatment, to correspond directly to a single patent, and there is rarely a one-to-one correspondence between legal entitlement to produce a finished product and access to technology covered by a single patent. On the one hand, in many countries, current routine vaccine production technologies are likely not to be covered by patents at all. On the other hand, producing a vaccine or pharmaceutical according to cutting-edge technologies may entail access to technologies covered by more than one patent, including patents at various 'upstream' and 'downstream' stages, as well as other technological inputs such as manufacturing knowhow, trade secrets and tacit knowledge. An actual vaccine or pharmaceutical is therefore better considered as a technology package of various inputs. Creating a legal pathway to producing such a product may involve freedom to operate analysis as well as negotiations over

various forms of licensing, cross-licensing, patent acquisition and transfer. Under some national laws, withholding reasonable access to vital core technologies may also lead in some specific circumstances to judicial or governmental interventions such as a compulsory license.

2.6 Patenting scenarios

This section sets out in concrete terms some practical patenting scenarios, based on empirical findings from an initial review of actual patenting activity. No opinion is made as to the validity of the patents.

2.6.1 Patenting a flu virus

A patent is sought on a flu virus as such: i.e. a claim is directed to a specified flu virus. Assessing its patentability would normally entail applying tests similar to the following checklist:

- Patentable subject matter: can a virus *as such* be patented? (e.g. is the virus considered a microorganism; are patents prohibited against genetic materials in the form occurring in nature?)
- Novelty: has information about the virus been published or disclosed in a form makes it available to the public?
- Do ethical or other *ordre public* issues apply? (e.g. would it be contrary to morality or prejudicial to health to commercialize the virus, such as a virus genetically engineered to be especially pathogenic?)
- What 'inventive step' or non-obvious act of invention on the part of the claimed inventor led to the virus? (e.g. is there an act of invention greater than simply characterizing a virus that occurs in nature?)
- What defined utility or industrial application has been identified for it?

Comment: A patent application on a wild virus as such is most unlikely to be considered eligible for patentability, and initial searches have not located any patents covering this subject matter. This should be contrasted with a newly engineerd genetic construct, such as a synthetic virus-like particle (VLP): there is a significant number of patent documents claiming new VLPs, methods of producing them, and vaccines produced from them.

2.6.2 Patenting a bare gene sequence.

A wild flu virus is obtained and its genome, or a portion of it, is sequenced. A patent is sought on a sequence identified within the virus: i.e. a claim is directed to specific DNA or RNA sequence or sequences. Assessing its patentability would normally entail applying tests similar to the following checklist:

- Is the DNA or RNA sequence itself subject matter for a patent – does it pass the test of being an invention? And does it contravene specific exceptions such as for naturally occurring genetic material?
    - E.g. to use the test applied in some national and regional laws, does the isolated sequence serve as a "technical solution to a technical problem"? Is the sequence isolated from its natural environment or produced by a technical process?
- Do ethical or other ordre public issues apply?
- Is the gene sequence novel, or has it been disclosed before (e.g. in a gene databank)?
- Was the identification of the sequence truly inventive? Was it obvious to the person skilled in the art to derive the disclosed sequence?
- What defined utility or industrial application has been identified for the sequence?

Comment: The simple act of isolating a gene sequence is generally not considered to be a patentable invention if it is a routine characterization of the sequence, and does not involve any inventive input by the researcher. Even if a sequence is isolated from its natural environment, and cloned for diagnostic, therapeutic or other practical use, this in itself would not make the sequence

patentable: there would have to be an 'inventive step' or a form of human intervention that was not obvious or routine, as well as a well defined new utility for the sequence.

2.6.3 Patenting transformed genetic material using a virus specimen

A wild flu virus is collected, and the specimen containing the virus is transmitted to a researcher who uses its genetic material when creating a genetic structure, which appears to be potentially useful for diagnosis or vaccine production – for example a virus like particle or a peptide chain that is harmless but has antigenic effect. A checklist of issues could include:

- Is the genetic structure itself new, in the sense that it had not been publicly disclosed to the public before (even if its origin or components have been disclosed to the public)?

- Was the creation of the new genetic structure truly inventive? Was it obvious to the person skilled in the art to create this structure for the intended purpose? For instance, was there an unexpected effect, running contrary to conventional expectations?

- What defined utility or industrial application was identified for the new sequence? Is it disclosed in such a way as to enable a skilled reader to replicate the claimed result? Is the invention claimed in such a way that all structures fitting within the patent claim would have the desired effect?

- Is the researcher bound by legal obligations arising from access to the genetic material, such as a specific contract governing the use and any application for patents on inventions resulting from that access? (While this would not affect the patentability of the invention as such, it may determine the entitlement of the applicant to seek or to hold a patent.)

2.6.4 Patenting transformed genetic material using sequence data

A wild flu virus is collected, and its sequence determined and documented. The published sequence is then used by a separate researcher in constructing a

new genetic structure, which is potentially useful for diagnosis or vaccine production. A checklist of relevant issues could include:

- Was the gene sequence available to the public in some way when the patent application was filed – in other words, was it then part of the 'prior art' against which the invention's novelty is assessed? Is the genetic structure, claimed as an invention, distinct from the published gene sequence, in the sense of putting new information in the public domain, beyond the original sequence?

- If the gene sequence had been published at the time of the invention, was it obvious in the light of background knowledge at that time to create the claimed genetic structure? Was this essentially following established procedures with predictable results, or was creation of the new genetic structure truly inventive? Was it obvious to the person skilled in the art to create this structure for the intended purpose? For instance, was there an unexpected effect, running contrary to conventional expectations?

- What defined utility or industrial application was identified for the new genetic structure? Is it disclosed in such a way as to enable a skilled reader to replicate the claimed result? Is the invention claimed in such a way that all structures fitting within the patent claim would have the desired effect?

Observation: patenting scenarios

Further versions of this paper will be enhanced with clearer depictions of actual patenting scenarios, along the vaccine development pipeline as described above. Each patent or patent application represents a distinct set of facts to be assessed in the light of the published prior art and common general knowledge at the time the application was filed. But general clusters of patenting activity can be discerned:

- Upstream inventions, such as genetic material directly derived from flu viruses
- Vaccine production technologies, such as new antigens and seed viruses, that indirectly make use of genetic material derived from wild strains
- Patents on downstream technologies that may in practice make use of genetic material derived from flu viruses, but do not assert that material to be part of the invention as such – such as new vaccine production technologies that inevitably need to incorporate extracts from new virus strains to meet emerging health needs

2.7 Patent rights, and exceptions and limitations

The implications of the patent system depend, ultimately, not upon the scope and character of the patents that are applied for or granted: in the end, the effect is felt from the way in which the rights granted under a patent are exercised and deployed to determine or constrain the acts of third parties. Hence any analysis of the impact of patents, and assessment of freedom to operate within the context of applicable patent law, must entail a consideration of the scope and effect of the exclusive rights available under a patent.

The rights afforded by a patent entitle the patent holder to take legal action to prevent others from undertaking a wide range of actions using the patented invention – such as making, using, offering for sale or selling patented products (such as commercial production of a vaccine covered by a patent); using a patented process (such as the use of a patented process for producing a vaccine); or using, offering for sale or selling a product directly obtained from a patented process (such as a vaccine produced by a patented process). Patent rights also cover importation of patented products or products from patented processes when imported for such purposes (although in some countries such rights of importation are 'exhausted' if the product was put on the market with the patent holder's approval in the exporting country).

2.7.1 'Reach through' effect of claims

A key practical issue in assessing the impact of patents relating to viruses and their genes is the extent to which a patent right on an upstream technology can 'reach through' to cover downstream applications of that technology. For example, some cases have concerned screening methodologies for identifying pharmacologically active agents, and have turned on whether a patent on such a method can constrain the use of pharmaceutical compounds identified through such methods. Regarding influenza vaccines, practical issues may arise in determining the reach through effect of patents on genetic material identified as methods of identifying or producing seed strains for vaccine production, and the subsequent downstream production and distribution of vaccines that make use of such seed strains.

Observation: reach through issues

At least as important as obtaining a factual overview of those patents that are relevant to the influenza virus and its genes may be reaching a practical

understanding about the 'reach through' effect of such patents – in particular, the implications of upstream patents on research technologies for the downstream production of vaccines.

2.7.2 Exceptions to patent rights

Patent rights are not absolute – in other words, the existence of the patent does not give its owner an absolute entitlement to prevent all other uses of the patented invention. Two general clusters of exceptions are mentioned here as of being of particular relevance, especially to preparedness for a flu pandemic:

Research exceptions: many national laws provide for exceptions to patent rights to allow researchers to make use of the patented invention for certain prescribed purposes relating to research rather than commercial application of the technology. For example, under some national laws, researchers may be entitled to make use of patented methods for producing attenuated viruses for vaccine production, either to test their effectiveness, or as part of their research in seeking new processes that improve or supersede that technology.

Regulatory approval exceptions: preparing for the production of a vaccine or pharmaceutical typically requires extensive regulatory approval steps. So-called 'Bolar exceptions' have been developed in particular to allow generic pharmaceutical producers to exercise a patent while it is still in force for steps related to obtaining regulatory approval.[17] This flexibility under TRIPS has been confirmed by WTO dispute settlement jurisprudence.[18] This may be relevant in taking steps to prepare for, but not to undertake, production of vaccines in the event of a flu pandemic.

Observation: regulatory exceptions

Regulatory use exceptions to patent rights may be of direct application in pandemic flu preparedness. Such provisions differ in national laws, but in essence they permit third parties to take steps reasonably related to securing regulatory approval for products (such as generic copies of vaccines or flu treatments), including pilot production runs if this is required for regulatory approval, while a patent remains in force – provided the preparations are indeed concerned with regulatory approval and do not amount to stockpiling or commercialization.

[17] Merck KGaA v. Integra Lifesciences, US Supreme Court

[18] Canada Pharmaceuticals case

2.7.3 Other use not authorized by patent holder

A key potential limitation on patent rights is the entitlement of government or judicial authorities to authorize, without the patent holder's consent, two forms of commercial-scale use and production: (i) government use authorizations (in which use by or on behalf of the government is undertaken for public purposes), or (ii) compulsory licensing as a means of addressing certain forms of market failure or uncompetitive behaviour in relation to the actual exercise of patent rights. Both forms of 'compulsory licensing' or 'use not authorized by the patent holder' have of course been the subject of significant policy debate and international negotiations (including amendment of the WTO TRIPS Agreement), specifically in the context of access to medicines, and that important debate is not replicated here. However, since such measures have been central to the debate over appropriate means of safeguarding equitable access to medicines, the same considerations clearly apply to the specific context of a response to an influenza pandemic.

A specific process concerning this provision stemmed from the WTO Doha Declaration on TRIPS and Public Health, which may be relevant to the subject matter of this paper. While space does not allow an extended discussion here, the WTO website summarizes the background to this development as follows:

> Article 31(f) of the TRIPS Agreement says products made under compulsory licensing must be "predominantly for the supply of the domestic market". This applies to countries that can manufacture drugs — it limits the amount they can export when the drug is made under compulsory licence. And it has an impact on countries unable to make medicines and therefore wanting to import generics. They would find it difficult to find countries that can supply them with drugs made under compulsory licensing.
>
> The legal problem for exporting countries was resolved on 30 August 2003 when WTO members agreed on legal changes to make it easier for countries to import cheaper generics made under compulsory licensing if they are unable to manufacture the medicines themselves. When members agreed on the decision, the General Council chairperson also read out a statement setting out members' shared understandings on how the decision would be interpreted and implemented. This was designed to assure governments that the decision will not be abused. The decision actually contains three waivers …

It is also pointed out that:

The 2003 waivers are interim; the ultimate goal is to amend the TRIPS Agreement itself, and a decision to do this was reached in December 2005, accompanied again by a chairperson's statement. The amendment — a direct translation of the wavers — enters into force when two thirds of members accept it.[19]

[19] See http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm02_e.htm#compulsorylicensing

3. CONCLUSION: POTENTIAL ROLES FOR THE PATENT SYSTEM

The following brief conclusions tentatively link the background material provided in this technical paper to the broader public policy context. It does not, however, seek to prejudge or pass comment on the key public policy issues concerning the influenza virus.

Existing patent systems present opportunities and constraints in the field of influenza. A balanced and effective patent system should by definition provide positive incentives and technology diffusion structures that sustainably promote new research and development in relation to the flu virus and vaccines against it, while also providing safeguards for effective dissemination of needed technologies. Potential roles of the patent system, that draw on fundamental principles of patent law and policy, are identified below. How to optimize these potential roles is a complex and challenging task. What amounts to an optimal response is likely to differ according to the development status of a country, according to the nature of the technologies involved, and according to where a specific patent lies along the pipeline of research, development, regulatory approval and commercial implementation.

Potential roles, which could ideally be optimized, include:

- clarifying and structuring technology partnerships: the patent is used to identify the specific contribution and freedom to operate of individual actors within a complex technology partnership, creating clearer definition of expectations and obligations to make technology available for defined purposes;
- inducing the investment of resources, particularly any necessary private sector resources, required to produce vaccines: the exclusivity afforded by patent rights can be a necessary inducement for the investment of capital and other resources (human, infrastructure, regulatory approval capacity) required to move from the stage of a scientific insight to a finished product that is safe, effective and economically feasible to produce and distribute;
- leveraging access to technology packages: strategic use of patents, including patents held by public sector institutions or public-private partnerships, can induce other players to provide access to other necessary technology and use rights, including those not covered by patents, such as confidential know how and regulatory approval files. A patent pool is essentially a structured version of this approach.
- transparency, or signaling trends and particular steps in vaccine research and development: the ease of access to patent information, together with the practical need to file early for

patent protection, means that patent information systems will serve as a useful monitoring mechanism for inventions that make use of flu strains and inventions that offer promise for new pathways for vaccine productions.

GLOSSARY

Adjuvant: a pharmacological agent that enhances the body's immune response to a vaccine, thus reducing the amount of vaccine that needs to be used for each individual dose; it improves the response to an antigen without itself functioning as an antigen

Antigen: a substance of external origin that stimulates the body's immune system, leading to the production of antibodies. It may include a virus, a virus like particle or a protein.

Avian flu: An epizootic form of influenza currently widespread among and readily transmissible between poultry.

Claims: That section of a patent document that sets out the legal scope of the subject matter for which exclusive rights are asserted, in other words the scope of the invention for which legal protection is sought. Claims are often amended and narrowed in the course of examination of a patent, for instance in the light of an examiner's objections to the original claims. So the claims as actually granted may be different from claims as first published in a patent application.

Epizootic: an infectious disease that appears in an animal population with a sharply increased rate above the expected levels. Avian flu is an epizootic, and is not an epidemic or pandemic.

Epidemic: an infectious disease that appears in a given human population with a sharply increase rate above the expected levels.

Freedom to operate: the scope to make use of a certain technology for certain defined purposes, determined by a range of factors: (i) legal scope of relevant patents; (ii) territorial scope of relevant patents and public domain status of technology in other countries; (iii) negotiated access in the form of licenses or assignments; (iv) other legal entitlements such as humanitarian waivers of patent rights; (v) exceptions and limitations such as regulatory use exceptions.

Gene: A single unit of heredity, the information encoded on a DNA or RNA sequence. A gene may provide the code for the production of a protein, such as an antigen, of use in preparing a vaccine.

Genetic material: defined in the Convention on Biological Diversity as "any material of plant, animal, microbial or other origin containing functional units of heredity."

Genetic resources: defined in the Convention on Biological Diversity as "genetic material of actual or potential value."

H5N1: The particular subtype of the influenza virus that causes avian flu, characterized by the two components that are present on the surface of the virus – 'H', or hemagglutinin (an antigen – a protein that stimulates an immune response), and 'N', or neuraminidase (an enzyme involved in the release of the virus from one cell to infect another). H5N1 is currently not an epidemic or pandemic, but is an epizootic among poultry.

Invention: The proper subject matter of a patent, not directly defined by international standards, but which is variously established under national law by positive definitions (e.g. "a solution to a technical problem"), by specific exclusions (e.g. exclusion of the human body) or by a mix of both.

IP management: The set of practices determining whether intellectual property protection is in practice obtained, and how intellectual property is managed, in order systematically to achieve defined objectives, such as a firm's corporate goals or a public research agency's institutional responsibilities. Approaches to IP management may therefore aim at attaining commercial objectives, public interest objectives, or a blend of both.

Non-obviousness: The requirement that, to be patentable, an invention should not be obvious, or should have an inventive step, generally assessed with reference to what would appear obvious to a 'person skilled in the art', such as a researcher in the relevant technological field. Actual tests and doctrines for applying this principle differ between national systems. This term is generally synonymous with 'inventive' or having an 'inventive step.'

Novelty: The requirement that, to be patentable, an invention should be 'new' or 'novel', generally in the sense that it should not earlier have been published or available to the public.

Ordre public: A general concept in the French language, that does not have a direct translation into English (hence it is often used untranslated; it is not the same as 'public order' in English). It is generally taken to refer to matters of fundamental public policy and the good order of society; yet this descriptive

characterization is for illustration only, and is not intended to provide a legal definition or interpretation (see also art. 27 2 of the WTO TRIPS Agreement).

Pandemic: an epidemic that is very widespread, across a continent or globally.

PCT: Patent Cooperation Treaty, an international system providing for international patent applications the Patent Cooperation Treaty (PCT) is a system for administrative cooperation through international patent *applications*, which must mature into independent patent applications and potentially patents in national and regional jurisdictions to have any legal effect).

Specimen: the physical tissue taken from a human or animal subject which may have viruses of interest present within it, present within infected cells contained in the specimen.

Virus: a sub-microscopic particle (most are too small to be viewed by optical microscopes) comprising genetic material (in the form of RNA or DNA sequences) contained within a protein coating (a 'capsid'). Viruses cannot reproduce themselves, but instead propagate through infecting a host cell, and using the host cell's reproductive mechanisms. A debate continues as to whether viruses can be considered 'organisms' (this has relevance for patent law, given references to patentability of microorganisms in many legal texts): generally, they are not considered to be life forms as such as they lack their own metabolism, but nonetheless are included in some definitions of microorganism.

> The term 'virus' may refer to an individual flu virus ('this cell is infected by a virus', or to a general type or subtype of virus ('the H5N1 virus', referring to the subtype in general)

Virus-like particle (synthetic): As a synthetic construct, a particle comprising proteins derived from a virus, that produces the same immune response as the virus, but is not itself infectious. Used in influenza vaccine research, and already approved for vaccines for human papillomavirus and the hepatitis B virus.