An Update on Intellectual Property Claims Related to Global Pandemic Influenza Preparedness

with Comments on the WIPO Patent Search Report on Pandemic Influenza Preparedness

8 April 2011

Prepared by:

Edward Hammond[1]

For

Third World Network

[1] E-mail: eh@pricklyresearch.com. Web: www.pricklyresearch.com

Introduction

As of March 2011, the wave of intellectual property claims over pandemic influenza vaccines that began in 2006 continues unabated. In some respects, patent claims on pandemic vaccines have accelerated since a Third World Network publication first analyzed this issue in 2007.[2] Direct claims on influenza genetic sequences and the proteins they encode, used in vaccines, impose a growing obstacle to access to influenza medicines, particularly in developing countries.

Before the recent development of new genetic and vaccine production technologies, and identification of the H5N1 pandemic threat, the field of influenza vaccine production was relatively unencumbered by burdens of intellectual property, which can prohibit access to technologies or require would-be vaccine manufacturers to engage in potentially lengthy and expensive license negotiations. Now, governments – especially but not exclusively developing country governments – are facing increasing problems as new vaccine technologies and therapeutic uses of influenza strains are more and more proprietary.

Not only do such claims impede access to technology and products produced with it, they are also often fundamentally unjust. Developing countries collect and share influenza viruses with WHO's Global Influenza Surveillance Network with the understanding that those viruses are to be used for public health purposes. Instead, they too often wind up being used to create proprietary products that developing countries cannot access or cannot afford.

There is no sign that the companies, governments, and universities that are lodging these claims are committed to the just and equitable sharing of benefits arising from pandemic influenza research, as stipulated in – and recently affirmed by - the Convention on Biological Diversity.

The October 2010 report of the Open Ended Working Group on Pandemic Influenza Preparedness[3] requested that the WHO Director-General ask WIPO to provide information on relevant patent claims. The WIPO report[4] was released on 1 April 2011 and comments upon it are included at the end of this paper.

This paper provides an alternative overview of recent PIP-related patent application activity a brief summary of selected recent and relevant patent applications.

---

[2] Hammond E. 2007. **Some Intellectual Property Issues Related to H5N1 Influenza Viruses, Research and Vaccines**. Third World Network. July. URL: http://www.twnside.org.sg/title2/IPR/pdf/ipr12.pdf.

[3] A/PIP/OEWG/2, p.2.

[4] WIPO 2011. **WIPO Patent Search Report on Pandemic Influenza Preparedness (PIP)-related Patents and Patent Applications**. URL: http://www.who.int/entity/csr/disease/influenza/Influenza_FullReport_01Apr2011.pdf

METHODS

The method of this study is straightforward and easy to understand. The International Patent Classification (IPC)[5] system was consulted to determine patent classes relevant to pandemic influenza. These classes were searched on WIPO's PatentScope database for patent applications. The searches particularly focused on A61K 39/145, the patent class to which applications for medicinal preparations (including vaccines) that include influenza viruses (and subunits) are assigned. A broader search was also conducted of patent classes covering influenza diagnostics, antibodies, and other related items.

The results of these searches are concisely displayed in graphics and tables on the following three pages. Data for 2011 is for the months January through March only. The term(s) and the classes of each search are clearly indicated on each page. Applications by year, by country of origin, and leading applicant companies are also provided. Information returned by the WIPO PatentScope database has not been altered, with the exception of the tables of top recent applicants. These have been updated to reflect corporate mergers.

On the basis of the PatentScope searches, supplemented by keyword searches of the US and European Patent Offices, a number of recent patent applications were selected for further examination.[6] A brief summary of each these applications is provided. These selections primarily focus on claims covering therapeutic uses of H5N1 and pandemic H1N1 influenza genes and proteins, but also include applications on pandemic-related adjuvant technologies, reverse genetics systems, human antibodies, and other pertinent items within the search scope.

This paper cites patent applications by their Patent Cooperation Treaty (PCT) publication number. Searches of the US, European, and other patent offices may identify corresponding national or regional applications.[7] National level application data is also available for some countries through WIPO's PatentScope or other national patent office websites, however, online patent application information remains limited to only certain countries.

[5] International Patent Classification website: http://www.wipo.int/classifications/ipc/en/

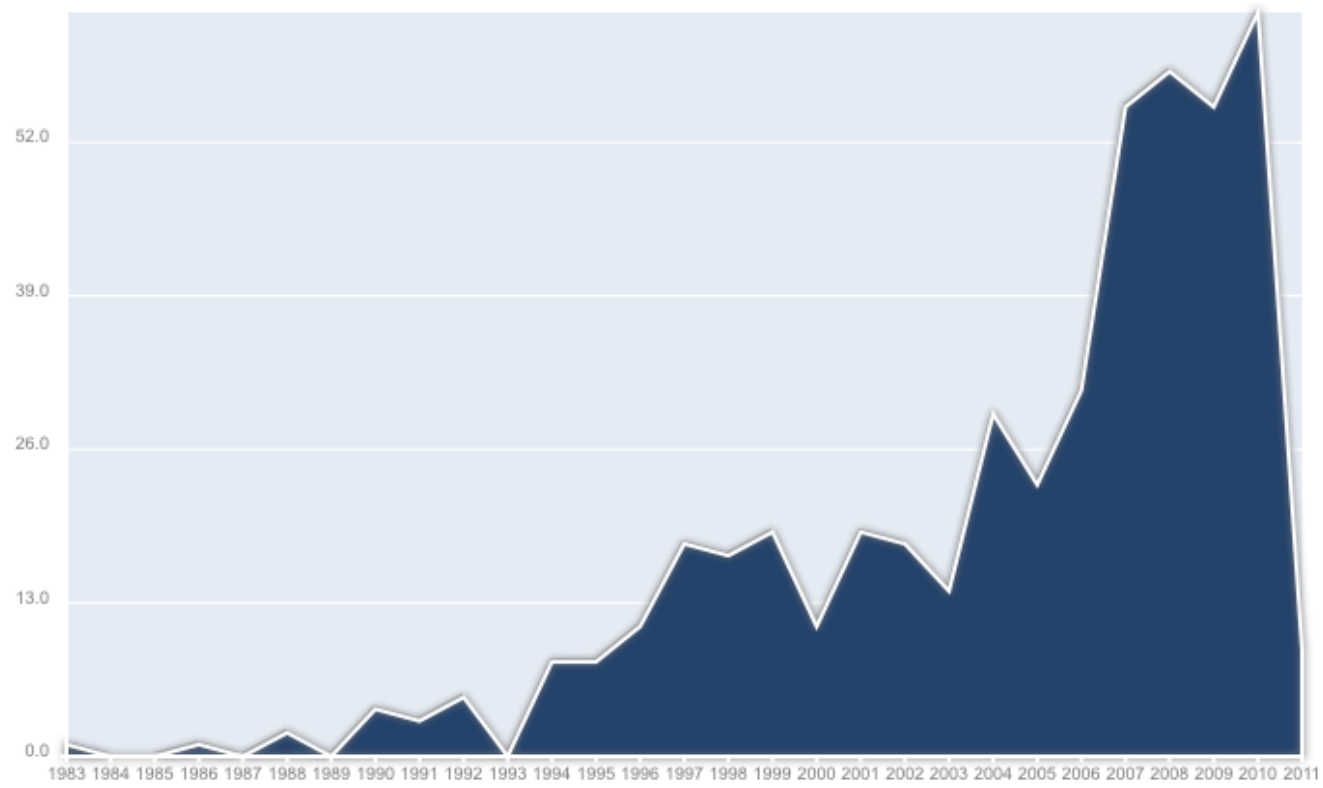
[6] A number of other patent applications are described in **Some Intellectual Property Issues Related to H5N1 Influenza Viruses, Research and Vaccines** (see footnote 1).

[7] US patent applications can be searched at URL: http://patft.uspto.gov. European patent applications can be searched at URL: http://ep.espacenet.com.

ALL PCT PATENT APPLICATIONS FOR INFLUENZA VACCINES (1983 – March 2011)

PCT Classification A61K 39/145 (Orthomyxoviridae). Source: WIPO / PatentScope

The 482 international applications in this category claim influenza A, B, and C vaccines for animals or humans. Claims may relate to adjuvants or other formulation technology, sequences, production, or a combination thereof.



Top Recent Applicants

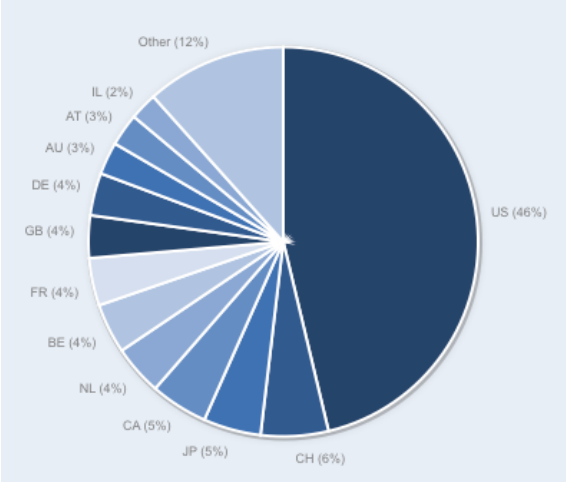
(Total for 2001-2011 YTD)

Novartis[8]	35
GlaxoSmithKline	15
Merck[9]	10
AstraZeneca[10]	8
Medicago Intl.	6
Crucell	6
Avir Green Hills	5

Recent Applications by Year

2001	19
2002	18
2003	14
2004	29
2005	23
2006	31
2007	55
2008	58
2009	55
2010	63
2011 (YTD)	9

Applications by Country of Origin

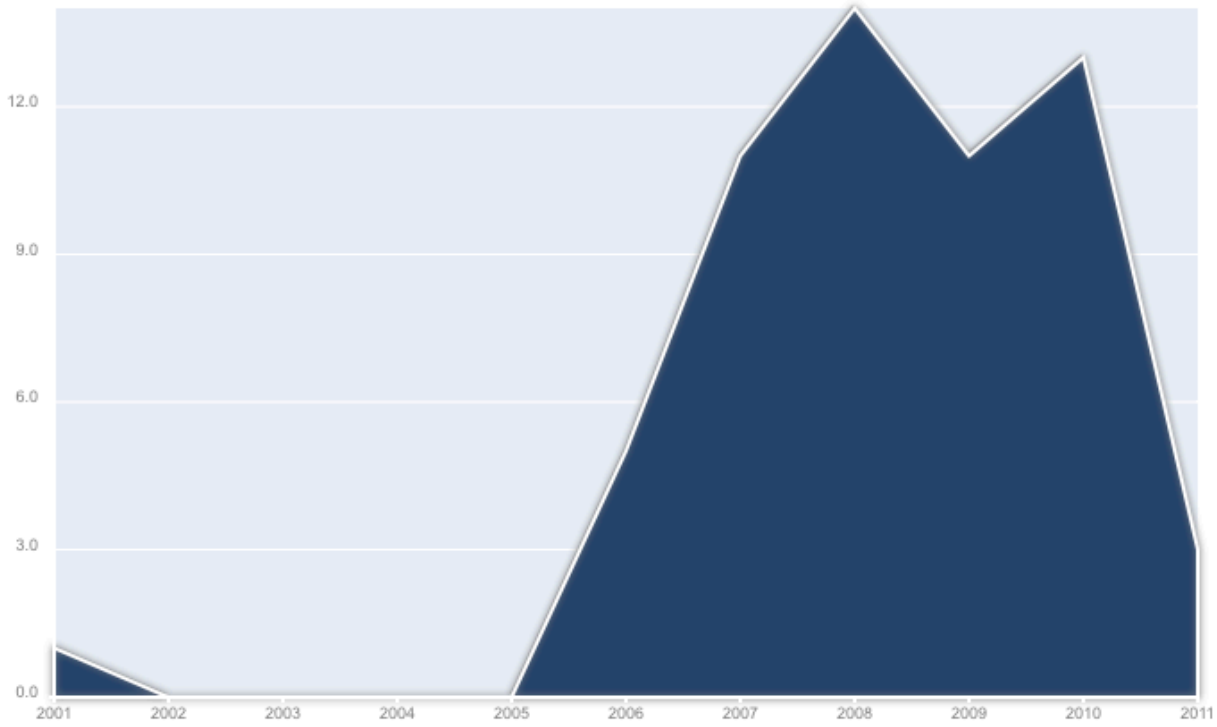


[8] Includes Chiron Corporation.
[9] Includes y Intervet.
[10] Includes Medimmune.

PCT PATENT APPLICATIONS FOR INFLUENZA VACCINES WITH THE TERM "H5N1" AND/OR "H1N1" APPEARING IN THE PATENT CLAIMS

PCT Classification A61K 39/145 / Source: WIPO / PatentScope

The 58 international applications matching this search claim influenza A vaccines for animals or humans. Claims may relate to adjuvants or other formulation technology, sequences, production, or a combination thereof. The were no matching applications before 2001.



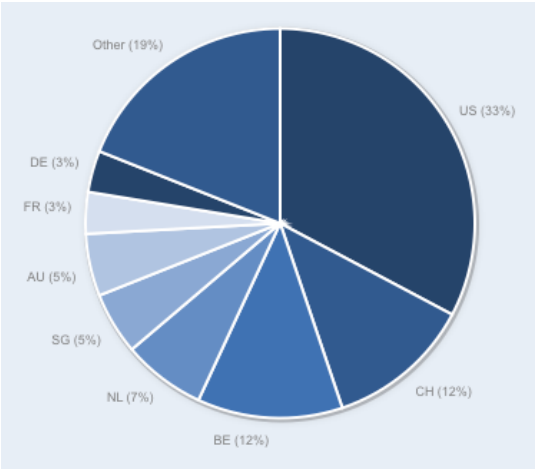
Top Applicants

Novartis	6
GlaxoSmithKline	5
Temasek Life Sci.	3
Crucell	2

Applications by Year

2001	1
2006	5
2007	11
2008	14
2009	11
2010	13
2011 (YTD)	3

Applications by Country of Origin

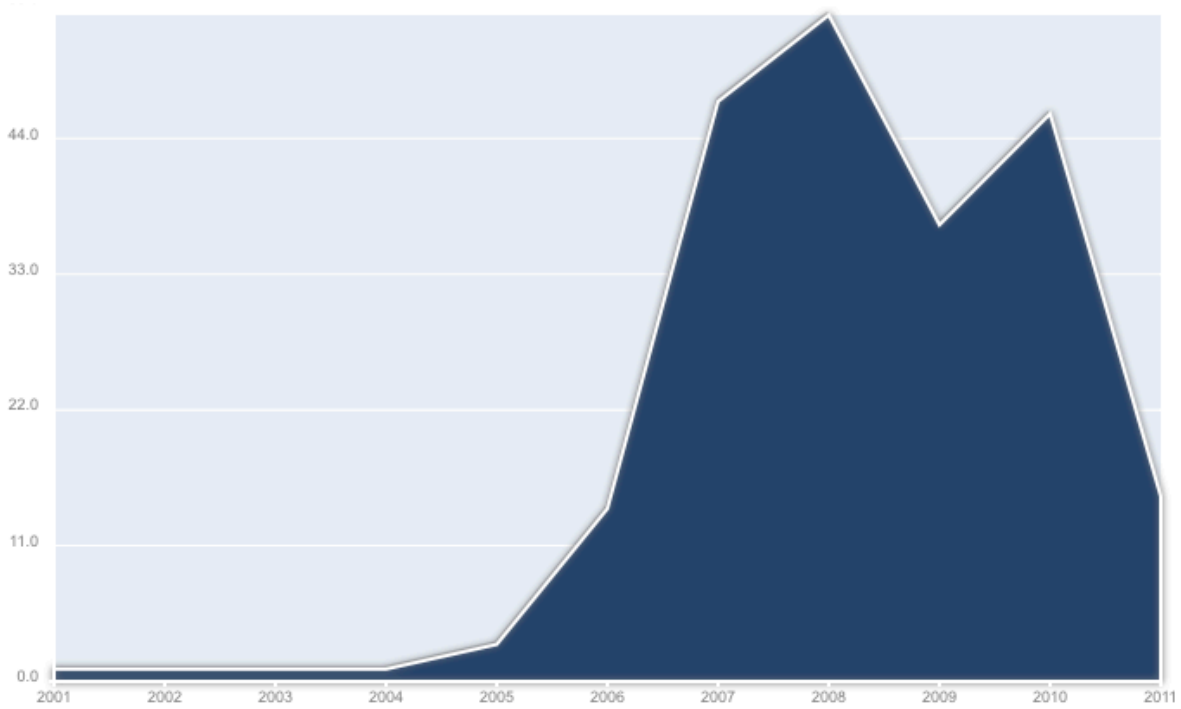


• Surge since 2007 in influenza vaccine applications making specific H5N1 and/or H1N1 claims continues unabated.

PCT PATENT APPLICATIONS FOR MEDICINES, VACCINES, MICROBES, PEPTIDES, NUCLEIC ACIDS, AND IMMUNOASSAYS WITH THE TERM "H5N1" AND/OR "H1N1" IN THE CLAIMS

PCT Classifications A61K/P, C07H/K, C12N/Q, G01N. Source: WIPO / PatentScope

The 220 patent applications matching this search cover a broader array of PIP-related technologies. These include diagnostics and therapeutics, including medicines and antibodies against H1N1 and/or H5N1 infection.



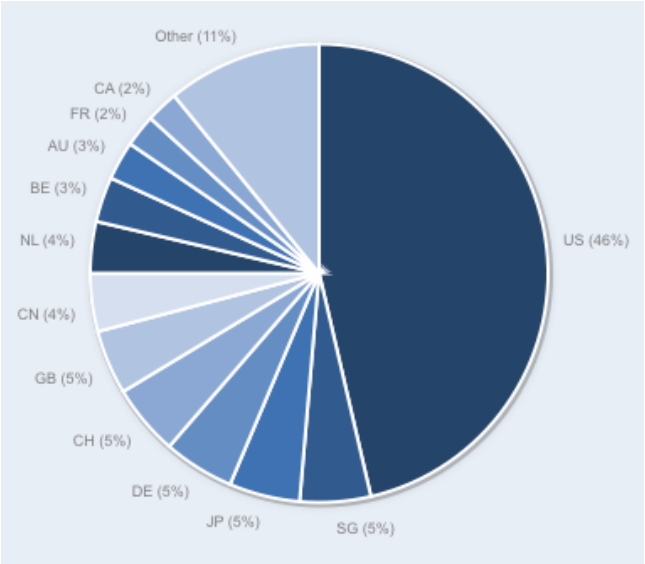
Top Applicants

Novartis	7
Temasek Life Sci.	6
Replikins (US)	6
GlaxoSmithKline	5
Crucell	4
Agency for Sci, Tech, and Research (SG)	4

Applications by Year

2005	3
2006	14
2007	47
2008	54
2009	37
2010	46
2011	15

Applications by Country of Origin



Summaries of Select Recent Patent Applications

The following pages briefly summarize more than a dozen recent patent applications in the patent classifications represented in the preceding charts. These summaries are only a small number of the total relevant applications. They have been selected to prioritize applications that cover use of H5N1 or H1N1 genetic material or proteins in vaccines.

It should be borne in mind, however, that influenza isolates and sequences are only part of the vaccine whole. Other types of increasingly proprietary technologies, such as those relating to adjuvants, reverse genetic systems (used to assemble vaccines), and cell culture techniques may prove essential for pandemic preparedness.

Indeed, so that the public health mission of WHO's influenza program may be fulfilled, it may be argued that allowing patent claimants access to influenza isolates and sequence data will only be just and equitable when those companies are obliged to freely transfer and/or affordably license related proprietary technologies that they own for pandemic preparedness use by developing countries.

WO/2010/148386
Swine-origin Influenza A (H1N1) Virus-like Particles and Methods of Use Thereof
Applicant: Novavax (US)
Published 23 December 2010

As the title suggests, this patent application claims use of 2009 H1N1 strains for the production of Novavax's virus-like particles (VLPs) that can be used as vaccines. These include Mexican and US strains from the 2009 outbreak. The patent application also claims use of the M1 protein sequence from the H5N1 strain A/Indonesia/5/05 for use in these H1N1 vaccines. Novavax is incorporating the Indonesian sequence into a variety of its products (see next page).

The publicly traded company has a market valuation of US $289 million and is staking much of its future on US biological defense program grants for influenza vaccines. The company has technology licensing agreements with Abbott Labs and GE Healthcare, has conducted trials and is seeking to license its H1N1 vaccine, made from a Mexican H1N1 isolate, in Mexico itself.[11] Terms of its planned sale of vaccine in Mexico do not appear to have been made public.

---

[11] Novavax Inc (2010). US Securities and Exchange Commission Form 10-Q. 6 August.

WO/2010/077986
Production of Influenza Vaccines
Baxter International
Published 8 July 2010

This patent application claims influenza vaccines that use HA and NA gene segments from one virus clade or type, and the remainder of the virus from another clade or type. Most of the claims are directed toward producing these vaccines in mammalian cell culture and constructing them in whole or in part from 30 different named H5N1 strains. These include animal and human H5N1 types from China, Vietnam, Indonesia, Thailand, Cambodia, Turkey, and Singapore.

With a market capitalization of over US $30 billion, in 2009 Baxter's sales topped US $12.5 billion.[12] The company has an agreement with Takeda Pharmaceuticals for manufacture and marketing of its vaccines in Japan.

WO/2010/077717
Modified RSV F Proteins and Methods of Their Use
Novavax
Published 8 July 2010

This patent application is primarily concerned with treatment of respiratory syncytial virus (RSV). It is pandemic influenza related, however, because it specifically claims use of the M1 protein/sequence of the H5N1 strain A/Indonesia/5/05 in the RSV treatments.

WO/2009/012487
Chimeric Varicella Zoster Virus-like Particles
Novavax
Published 22 January 2009

Similar to the preceding patent application, this application claims the A/Indonesia/5/05 M1 protein/sequence for use in Varicella Zoster (VZV) vaccines. (VZV is the causative agent of chickenpox and shingles.)

These patents from Novavax are clearly related to pandemic influenza as they claim use of H5N1 sequences. Yet they are not oriented toward the diagnosis or treatment of influenza itself. Instead, influenza sequences have been utilized to help treat other infectious diseases. These patents signal the importance of bearing in mind that biological materials shared for pandemic influenza preparedness purposes need to be protected from inappropriate commercial and other uses.

---

[12] NASDAQ (2011). Baxter International Company Finances. http://www.nasdaq.com/asp/extendfund.asp?symbol=BAX

WO/2010/006452
New Influenza Virus Immunizing Epitope
Medicago (CA)
21 January 2010

This patent application claims virus like particle influenza vaccines manufactured in plants, specifically including VLPs with the HA protein encoded by "H5 Indonesia". The patent application provides the sequence of the HA gene of A/Indonesia/5/05; but the imprecise language of the claim is unclear. It may be interpreted to be specific to A/Indonesia/5/05 or could encompass all Indonesian H5 HA genes/proteins. WIPO review of this patent application has questioned the novelty of its claims, however, the Canadian company has several other influenza-related patent applications and is advancing its vaccine in human trials.

WO/2009/092038
Influenza DNA Vaccination and Methods of Use Thereof
US Government
23 July 2009

This US government patent application claims H5 DNA vaccines constructed from human and animal H5N1 viruses collected in Indonesia, China, Nigeria, Vietnam, South Korea, Turkey, Thailand, and Iraq. The DNA constructs of the claim include two or more different HA segments. The application is particularly focused upon, but not limited to, H5N1 vaccines. Particular combinations of HA segments from different H5N1 isolates are claims, for example, a vaccine "wherein the DNA construct encodes H5 HAs from A/Anhui/1/2005, A/Indonesia/05/2005, and A/chicken/Nigeria/641/2006" (Claim 27).

This patent application is notable in more than one respect. Firstly, it presents specific claims over use of Iraqi, Egyptian and Nigerian HAs, in addition to the Asian isolates more frequented claimed in patent applications. Secondly, the patent application is made by the US Secretary of Health and Human Services, the same ministry that operates the WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza at the US Centers for Disease Control (CDC).

WO/2009/012489
Avian Influenza Chimeric VLPs
Novavax
22 January 2009

This Novavax patent application claims a manner of increasing the efficiency of production of virus like protein (VLPs) and use of the VLPs as influenza vaccines. Specifically, it claims use of the HA and/or NA gene from A/Indonesia/5/05 in the vaccines, including genetically modified variants. The VLP production system includes use of an avian influenza M1 gene, and the A/Indonesia/5/05 M1 sequence is again specifically claimed.

WO/2011/031125
Recombinant Proteins that can be Expressed in Escherichia coli as Active Ingredients of Vaccines Against the 2009 Outbreak H1H1 Influenza A, and Production Method Thereof
ITESM (MX)
17 March 2011

This patent application, from a Mexican university, claims recombinant E. coli used to produce vaccines against H1N1 for use in mammals. The E. coli incorporate antigenic H1N1 HA capsule protein sequences. The source of the sequences appears to be a 2009 Mexican isolate identified, in non-standard nomenclature, as "MX/a/2009/009565".

WO/2011/003100
Compositions and Methods for Diagnosing and/or Treating Influenza Infection
Massachusetts Institute of Technology
Published 6 January 2011

The unsettling core invention claimed in this patent application is a method by which the extreme infectivity exemplified by the recreated 1918 pandemic influenza strain (A/South Carolina/1/1918) can be transferred to other flu strains, particularly Mexican and US 2009 pandemic H1N1 isolates. The increase in infectivity, which the inventors claim can be over 1000-fold, is accomplished by mutating the HA genes of less infective isolates to increase their binding to receptors in the human upper respiratory tract.

The patent application claims, as matter, H1 HAs mutated to be more infectious: Claim 5: "*An engineered Hl HA polypeptide that causes an influenza virus to demonstrate a similar level of infectivity of humans as is demonstrated by A/South Carolina/1/1918*..."

While the inventors cite a number of possible vaccine and diagnostic uses of the technology, public health concerns about use of this technology should be considerable. Accidental release of virulent influenza strains (or novel strains bearing such a modified HA) would pose the risk of a man-made pandemic.

As accidents such as Baxter and Avir Green Hills' accidental distribution of H5N1 in 2009 demonstrate,[13] this is arguably an example of research on PIP materials that simply should not be permitted.

---

[13] PROMED. 2009. **Avian Influenza, Accidental Distribution Czech Republic ex Austria**. 29 February. URL http://www.promedmail.org/pls/otn/f?p=2400:1001:80787::::F2400_P1001_BACK_PAGE,F2400_P1001_ARCHIVE_NUMBER,F2400_P1001_USE_ARCHIVE:1001,20090226.0801,Y

WO/2011/012999
Reverse Genetics Systems
Novartis
Published 2 March 2011

This patent application claims a new reverse genetics system for the production of influenza viruses in cell culture. It is claimed that this system is faster and more efficient than existing systems, which are also proprietary. The importance of reverse genetics systems lies in their ability to quickly assemble "custom" vaccine viruses that involve genetic combinations that would be difficult and/or time-consuming to achieve using traditional reasssortment processes (coinfecting cell cultures with different viruses).

Access to reverse genetics technology is important for developing countries both because they many need it to create their own vaccine strains or because they may wish to produce vaccine from seed strains produced by others using reverse genetics (and thus potentially requiring a license from the patent holder).

Novartis' 2010 gross sales exceeded US $51.5 billion. After expenses, Novartis shareholders enjoyed $11.7 billion in pretax profits. That's more than the gross domestic product of H5N1-affected Cambodia, whose population is double that of Novartis' home country of Switzerland. And whereas in 2009 Switzerland quickly secured company commitments to quickly provide 13 million doses of H1N1 vaccine for its 7.7 million people,[14] even through Cambodia was lucky to be one of the largest recipients of H1N1 vaccine donations from WHO, the 2.7 million doses it received[15] sufficed to vaccinate less that 1/5 of Cambodians with a single dose. (Fortunately, the pandemic proved less serious than feared.)

WO/2011/009864
Novel Influenza Virus
Avir Green Hills Biotechnology (AT)
Published 27 January 2011

This patent claims attenuated reassortant influenza vaccine viruses with modified NS and PB1 gene segments. The patent claims that the resulting viruses, which do not code functional NS or PB1 proteins, make the vaccine viruses more immunogenic and attenuate their virulence. Live, replication-incompetent versions of these viruses, the company says, are suitable for vaccines (particularly for intranasal administration).

The Austrian company, whose research is supported by European Union public grant funding, has prepared such vaccine strains utilizing H5N1 viruses from Vietnam, Indonesia, Hong Kong, and Russia, and has selected the Vietnamese variant for clinical trials.

---

[14] Swissinfo. 2009. **H1N1 vaccine campaign to begin mid-November**. 30 October.
[15] WHO. 2010. **Final Pandemic (H1N1) 2009 vaccine deployment update**. 10 November.

WO/2010/151673
Swine Flu Hemagglutinin Variants
AstraZeneca
Published 29 December 2010

Filed less than three months after the 2009 outbreak of H1N1 was declared an international public health emergency by WHO, this ambitious AstraZeneca patent application, with 341 claims, in essence seeks to lay company claim to the HA gene of 2009 H1N1. Specifically, it claims the HA protein and gene of A/California/7/09, an early 2009 H1N1 isolate, including various mutants. It also claims H1N1 HA genes 95% or more similar, presumably thereby effectively encompassing many other recent H1N1 pandemic HAs.

London-based AstraZeneca grossed US $32.8 billion in 2009, resulting in a $10.8 billion in pretax income.

WO/2010/125461
Adjuvanted Vaccines for Protecting Against Influenza
Novartis
Published 4 November 2010

The lead inventor in this new patent application from Swiss biomedical giant Novartis is none other than Klaus Stohr, the former leader of WHO's Global Influenza Program. The claim covers a variety of H1N1 vaccines that use an oil in water adjuvant (such as squalene).

The cleverly worded claims of this patent application do not specify a particular vaccine strain sequence or protein. Instead, they encompass an entire class of HA genes, when used in an adjuvanted vaccine. The patent application attempts this bold claim by providing the HA sequence of an early 2009 H1N1 isolate from California, and that of a non-pandemic 1983 Chilean influenza isolate. The patent then claims adjuvanted vaccines that use <u>any</u> HA gene that is "*more closely related*" to the pandemic California isolate than its Chilean counterpart. This would encompass all HA genes from 2009 pandemic isolates and quite possibly many others in years to come.

WO/2011/003920
Adjuvanted Influenza Vaccine and Use Thereof
Abbott
Published 13 January 2011

This patent application by Abbott Biologicals covers influenza vaccines, particularly H1N1 and H5N1 vaccines, which use subunits, or modified subunits of toxins as adjuvants. These pieces of toxins, which might include ricin, cholera, diphtheria, shiga, and other dangerous

substances, are not themselves harmful. Instead, the company claims, they increase response to influenza antigens in the vaccine.

Abbott's adjuvant is one of a number of competing proprietary technologies to boost the effectiveness of influenza vaccines. These are potentially important technologies for two reasons. First, they may increase the success rate of vaccination by triggering a more effective immune response. Secondly, they may reduce the antigen doses in vaccines, allowing the same amount of bulk antigen to vaccinate more people, potentially increasing the speed and efficiency of vaccination programs.

Whether or not Abbott's new adjuvant proves critical, government need to bear in mind the importance of access to proprietary adjuvants as they may be a critical part of pandemic response.

WO/2009/036157
Donor-Specific Antibody Libraries
Sea Lane Biotechnologies
Published 19 March 2009

This patent application, by a small California company, claims 146 human antibodies to H5N1 infection. The antibodies were obtained from blood and bone marrow samples of eighteen human survivors of a 2005 H5N1 outbreak in Turkey. Of the eighteen people, H5N1 infection was confirmed in six by WHO or the Turkish Ministry of Health. The remaining twelve were treated for suspected H5N1 infection.

Neither the patent application nor any other information available from Sea Lane explains the circumstances under which the human tissue samples were obtained or how they came into Sea Lane's possession.

The company is testing the antibodies to determine their reactivity to the HA of other influenza strains, including Indonesian and Vietnamese H5N1 isolates as well as 1918 influenza. Having filed for patent, the company is now flogging the human proteins on its website, which states "*Sea Lane is open to discuss business models that allow leverage into these resources.*"

Comments on the WIPO Patent Search Report on Pandemic Influenza Preparedness

The preceding pages seek to provide a rational and straightforward assessment of patent activity relevant to pandemic influenza preparedness by providing a statistical overview of patent trends followed by representative examples to the types of patent claims that are presently being made.

At the request of the WHO Pandemic Influenza Preparedness Open Ended Working Group (PIP OEWG), the World Intellectual Property Organization (WIPO) has also prepared a study assessing pandemic influenza-related patent applications.[16] The report, titled *WIPO Patent Search Report on Pandemic Influenza Preparedness (PIP)-Related Patents and Patent Applications*, was published on 1 April 2011.

The following comments offer critical perspective on the WIPO study and some comparisons with this paper.

Broadly Confirmatory but Flawed

Broadly speaking, the WIPO study confirms the perspective of this report. WIPO identifies dozens of patent applications over potentially pandemic virus genes and sequences, and/or their use. "Freedom to operate" analysis was beyond WIPO's charge, but it is clear that these patent applications impinge upon the ability of developing and other countries to respond to an influenza pandemic.

The WIPO study identifies 32 patent families of direct relevance within its scope, and 42 more patent families[17] that are "*subject to interpretation*", by which WIPO means that "*sequences of H5N1 and H1N1 are only one element of the invention*" (discussed below).

In characterizing the patent applications that it identifies, WIPO predictably prefers to emphasize the possibility of their use by developing countries through licenses or other agreements with the patent owners, rather than discuss how the claims create impediments to preparing for pandemics. Use of these proprietary technologies by developing countries as envisaged by the WIPO authors, however, assumes that they will be affordable, or available at all, in the event of a new pandemic. This assumption appears to be at odds with recent developing country experience with H5N1 and H1N1.

If in general the WIPO study may be taken as confirming the concerns expressed by this report, WIPO's approach was also marred by an overly narrow scope and by flaws in its patent search and categorization methods. These problems diminish the usefulness of the WIPO study by limiting and miscategorizing its results.

---

[16] WIPO (2011). **WIPO Patent Search Report on Pandemic Influenza Preparedness (PIP)-Related Patents and Patent Applications**. 1 April.

[17] The numbers used in the WIPO vary slightly between the text and its annex. Here, a count of the number of patents cited in the annex is used.

Restricted Scope

With respect to scope, this paper has emphasized that the patent applications that are related to pandemic influenza preparedness are not only those that claim influenza genetic sequences and/or their use. Claims on a variety of other related subject matter, such as influenza vaccine adjuvants, influenza reverse genetics systems, and influenza cell culture have direct bearing on governmental preparedness efforts.

Yet these latter types of patent claims were expressly excluded from the WIPO report and do not figure within its results. That is because WIPO and WHO determined to limit the search to "*patents or patent applications claiming inventions comprising the virus, a component, or a derivative of the virus, for diagnostic, therapeutic, or prophylactic purposes*" filed since it became apparent that H5N1 and, later, H1N1 posed a pandemic threat.

Thus, by limitations in scope, the WIPO study omits many kinds of important influenza vaccine technologies, resulting in an undercount of relevant intellectual property claims.

Monoclonal Antibodies as an Example of the Problems with Scope

WIPO takes a narrow view of its already limited searches, ignoring patent applications that seem to meet PIP OEWG's intent and even its restricted scope. The first page of the WIPO report explains that during its patent search (for H5N1 and H1N1 keywords), "*most patent families* [identified] *fell outside the specific objective of the study and claimed, for example, monoclonal antibodies…"* (An example of such an application, by Sea Lane Biotechnologies, is discussed on page 13 of this paper.)

Excluding monoclonal antibody claims is a rather remarkable omission in view of the fact that monoclonal antibodies are clearly virus-derived (cannot be produced without the virus) *and* can be used both for influenza diagnosis and treatment. WIPO's decision to ignore these patents indicates an excessively exclusionary approach, as if low counts of relevant patents were an intended result.

Novavax Patent Applications as Another Example of Problems with Scope

The Novavax patent applications WO2010077717 and WO2009012487 were not identified by the WIPO study, indicating another failing in its scope. These patent applications, discussed on page 8 of this paper, claim use of M1 gene components from A/Indonesia/5/05 in varicella (chickenpox) and respiratory syncytial virus (RSV) vaccines. These are presumably not the only instances of such omissions.

While it is true that varicella and RSV vaccine technologies would be unlikely to have significant use in pandemic influenza response, these claims are relevant to PIP OEWG. They are relevant because they are proprietary claims on materials provided to the WHO Global Influenza Surveillance Network and, as such, raise issues of benefit sharing.

Should WHO Member States allow companies to patent PIP virus materials for other purposes at all? If they did, shouldn't such patent holders have an obligation to share benefits with Member States, to assist the overarching purpose of pandemic preparedness?

Such patent claims need to be considered by the PIP OEWG if governments want to ensure that viruses provided to the WHO network are not turned into proprietary resources for other purposes.

The "Subject to Interpretation" Category: A Dubious Criterion

WIPO's categorization of patent families again results in reducing the number of patents identified as relevant. Here the culprit is subjective interpretation of inventor intent. The study assigns a number of patent families to a "*subject to interpretation*" category. This category, called "*second tier*", is implied to be of lesser importance than those patent families deemed to be directly relevant. The criterion used to define this category was if the application claims "*sequences of H5N1 and H1N1* [as] *only one element of the invention*".

One part of a few or many "elements" of the invention, a more logical criterion would have been the simple and relatively objective test of whether the patent application claims virus sequences and/or their use or not. The WIPO paper attempts to draw a distinction between patent applications that claim sequences "in isolation" (or "as matter") versus those that claim viruses, or parts thereof, embodied in vaccines or diagnostics. While this distinction can be objectively appreciated, its significance may not be very great. This is because, in practical terms, a sea of patents covering all manner of uses of potentially pandemic viruses is, in the real world, is tantamount to a sea of patents covering specific gene sequences.

It is also the case that patent applications are frequently both – claiming both sequences as matter and pandemic genes (defined as sequences or in other ways) as used in a vaccine or diagnostic. The final extent of the claims depends on patent examiners and may vary by jurisdiction. Sequence claims, for example, have been easier to obtain in the United States; but the same patent application, in a modified form still claiming use of those sequences, may be easier to obtain in Europe or other jurisdictions.

Thus, what WIPO describes as a "second tier" category of patent claims includes a number of applications that clearly are of importance to the PIP OEWG. For example, these include the Novartis patent application WO2010125461, discussed on pages 11-12 of this report. On detailed analysis, and depending on the evolution of both influenza and technology, some of the "*subject to interpretation*" patents may prove of more direct interest than others. But their categorization as secondary by WIPO is potentially misleading. These so-called "*second tier*" claims may prove to be of primary importance.

Issues in Sequence-based Searching

While WIPO employed multiple methods to identify patent claims, to the extent that its searches rely on the gene sequence search system called BLAST (Basic Logical Alignment Search Tool), there are methodological issues that merit discussion. While BLAST searches can identify many relevant patent applications, including some that this study may have missed, BLAST searches assume that a relatively specific influenza sequence will be found in a patent application if that patent application claims its use.

The assumption is flawed. There are a variety of ways to write patents so that they assert claim to using particular virus sequences without specifically spelling out those sequences in the patent document. BLAST searches do seek out similar sequences to that searched; but still may miss such claims.

Two claim-writing strategies to cover diverse influenza genetic sequences without providing their "letters" are used in patent applications identified in this paper. One is to claim a specific sequence, and to then assert ownership of other sequences that are similar. The exact degree of similitude is often left flexible in the patent application. For example, the patent claim may say, "We claim [a specific sequence] and any other sequence that is 80%, 85%, 90%, 95%, 97%, or 98% homologous". A final determination of the percentage to be permitted is made before the patent is issued. Similarly, pages 11-12 of this report describe a patent claim-writing strategy used by Novartis that has a similar intent. A BLAST search may not identify applications with claims that are so structured.

Misleading Presentation of CAMBIA Study

On pages 9-10, the WIPO study discusses, at length, a 2008 paper by the Australian organization CAMBIA. The CAMBIA paper found relatively few patent claims on H5N1 sequences, a finding WIPO reports. The BLAST-based methodology of the CAMBIA study, however, was particularly poorly designed and susceptible to omissions. Regrettably, the CAMBIA study is not reliable as search design excluded many relevant patents.

Responding to criticism, the CAMBIA authors have conceded that "*there are many techniques for filing invention disclosures that render the searchability of DNA or protein sequences very difficult*" and "*finding DNA or protein sequences disclosed in or claimed in patents is extraordinarily difficult*"– their way of admitting methodological problems.[18]

WIPO's discussion of the CAMBIA study presents its results; but does not explain the serious shortcomings that have been identified in the CAMBIA methods. It does not seem proper for WIPO to cite the CAMBIA study at such length without identifying its flaws.

Determination of Appropriate Sequences to Search

In addition to the other drawbacks of BLAST-based patent searching in this context, based on the description of how the WIPO study was conducted (pages 14-15 of the WIPO paper), it is unclear if an appropriate set of H5N1 sequences was searched.

According to WIPO, it searched representative sequences including the HA genes of five H5N1 strains from three Asian countries. It is unclear what other sequences were searched. Only one of the strains mentioned in the WIPO paper (A/Anhui/1/2005) has often been mentioned in patent applications, while others that frequently figure in patent applications – notably A/Indonesia/5/05 and A/Vietnam/1203/04 – do not appear to have been

[18] CAMBIA (2008). **Influenza Genome Executive Summary**. URL: http://www.patentlens.net/daisy/influenza/4132.html (accessed 6 April 2011).

specifically searched (although these applications might have been caught, depending on the – not fully explained – methods used).

The ambiguity of WIPO's description of its methods makes conclusions difficult. However, logical manners of selecting sequences to search appear to have been ignored. For example, a specific BLAST search of the sequences of the H5N1 influenza strains that have been selected by WHO for use in vaccines seems highly appropriate for the purposes of the WIPO study. This search does not appear to have been conducted. As it stands, there is inadequate information provided to assess the method for selecting sequences to search.

Finally, it appears that only HA gene sequences were searched. A number of patent applications, however, lay claim to other parts of the influenza genome. These include NA sequences and the M1 sequences claimed by Novavax. In fact, some companies developing influenza vaccines are increasingly focused on vaccines targeting less variable, "conserved" parts of the influenza genome, increasing the chances that they will lay claims to non-HA sequences because those genes change more slowly than HA.

Closing Comments

Ironically, the WIPO report does not significantly rely on WIPO's own system for categorizing patents by subject matter – the International Patent Classification system (IPC), which was used to prepare this report. The IPC categories contain, for example, a specific classification for influenza vaccines to which relevant patent applications are assigned. The WIPO report does not explain why the IPC system was not relied upon (or its national or regional equivalents, such as US patent classes).

The WIPO report concludes with a number of exculpatory sounding comments about the patent applications, and suggests that broad intellectual property management frameworks exist in which PIP-related intellectual property might be shared. This beneficent outlook on patents might be expected from WIPO; but it does not appear that any of these ideas have been significantly applied to pandemic influenza in practice.

In summary, despite it limited scope and methodological issues; the WIPO study is confirmatory of the concerns raised in this paper, as it identifies a large number of relevant patent claims. Further, there are many reasons to expect that if WIPO adopted a more appropriate search scope and methods less prone to omissions an "downcategorizing", that WIPO's results would include even more patent applications on influenza genetic resources and their use that could prove problematic for developing countries in the event of a pandemic – and highly profitable for the companies and others that claim exclusive right to them.