

Achieving Clinical Equality in an Influenza Pandemic: Patent Realities

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ABSTRACT

A twenty-first century novel influenza A (H1N1) pandemic is currently unfolding, and the eventual scope of this public health crisis is not clear. In addition, ongoing surveillance of the avian influenza A (H5N1) virus reveals outbreaks of human-to-human transmission of the virus with significant mortality. Effective pandemic management depends on pharmaceutical intervention with two different clinical objectives: the generation of an immune response to specific viral strains (vaccination) and the reduction of viral replication in an infected individual (antiviral administration). The ability to offer pharmaceutical interventions for a public health crisis depends on three factors: development, capacity, and access. Pharmaceutical measures must be developed, capacity must be established, and access must be ensured.

This Article discusses the three nodes of patenting that influence the availability of pharmaceutical countermeasures in an influenza pandemic. Identification of the causative influenza virus is the first step in pandemic management. The virus and its RNA sequence are both knowledge assets and physical inputs required for vaccine design. Vaccine development, therefore, will be influenced by any patents on the genetic sequences or proteins of the pandemic virus, as well as on novel methods for vaccine production, the actual vaccine, or adjuvant technology, all of which are relevant to the assembly of a working vaccine on short notice. Pharmaceutical treatment of influenza infection during a pandemic could also rely on the use of patented antiviral drugs whose efficacy may be revealed as the pandemic unfolds. Unlike vaccines, these are not generally developed *de novo*

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for a pandemic, but their availability could be dependent on the exercise of patent rights by market incumbents. Patent rights could control capacity, which may determine access.

Pandemic planning must consider how patenting can influence development, capacity, and access to pharmaceutical interventions. National and international public health authorities are slowly integrating intellectual property considerations into pandemic planning. Further integration will anticipate the emergence of patent claims, identify any relevant patents, encourage access norms, and consider the use of legal mechanisms that could alleviate patent-mediated obstacles to the availability of critical products and methods that may be patented.

This Article will discuss the patent nodes relevant to vaccine development and to antiviral distribution during a global influenza pandemic, identify where such patents may facilitate or inhibit the availability of pharmaceutical countermeasures, and offer preliminary observations on the currently emerging novel H1N1 pandemic. The goal of international clinical equality is essential for the eradication of an influenza pandemic, and strategies for its achievement can also be applied to other diseases.

I. INTRODUCTION

Viruses have coexisted with humans throughout history, either passively as biological background noise or as microbial enemies capable of causing both treatable and untreatable illnesses. Public health menaces such as smallpox, yellow fever, measles, Ebola, HIV, and polio are the result of viral infections that spread through populations, with the attendant consequences of morbidity and mortality.¹ A striking feature of viral diseases is the contrast between the seemingly simple nature of the infectious agent and the magnitude of the disease toll that it exacts.² For example, the HIV virus has nine genes³ and influenza virus has eight genes,⁴ both far fewer than the estimated 25,000 genes in the human genome.⁵ This apparent genetic simplicity, however, does not minimize the difficulty of developing effective prevention and therapeutic strategies.

¹ See MICHAEL B. A. OLDSTONE, *VIRUSES, PLAGUES AND HISTORY* 3–6 (1998).

² *Id.* at 8 (noting that viruses are “nothing more than a speck of genetic material and a coat of protein molecules.”).

³ 2 S.J. FLINT ET AL., *PRINCIPLES OF VIROLOGY* 170 (3d ed. 2009).

⁴ 1 *id.* at 512.

⁵ Int’l Human Genome Sequencing Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 *NATURE* 931 (2004).

Influenza virus has a significant impact on human health. It is not only responsible for annual seasonal outbreaks and periodic pandemics, but it also draws the public health community into an ongoing relationship involving both manageability and crisis. The nature of an influenza public health crisis is a function of virulence of the particular viral strain.⁶ An annual influenza season is characterized by the global spread of a viral strain with a fairly predictable pattern of disease and mortality, for which an annual vaccine is developed to contain the spread and lessen the burden of illness.⁷ Nonetheless, it is estimated that approximately 36,000 deaths occur in the United States each year from seasonal influenza.⁸

Occasionally, an influenza strain particularly lethal to humans develops, appearing first as an animal influenza strain that jumps to a human host, and then becoming capable of human to human transmission. Influenza is capable of causing a pandemic, which is a public health crisis characterized by the following conditions: a new viral strain emerges to which humans have no immunity; the viral strain infects humans and causes illness; and sustained transmission occurs among humans.⁹ Several pandemics have occurred in the last century. In the 1918 influenza pandemic, an estimated 675,000 Americans died as the result of an influenza virus with a relatively high mortality rate of 2.5 percent.¹⁰ Later influenza pandemics occurred in both 1957 and 1968.¹¹

Influenza is a segmented RNA virus with its genome divided among eight segments.¹² Influenza is classified into subtypes A, B,

⁶ Virulence is defined as the ability of a virus to cause disease, or pathogenesis. 1 FLINT ET AL., *supra* note 3, at 40.

⁷ See generally ANTHONY E. FIORE ET AL., PREVENTION AND CONTROL OF INFLUENZA, RECOMMENDATIONS OF THE CENTERS FOR DISEASE CONTROL ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) (Aug. 8, 2008), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5707a1.htm>.

⁸ Approximately 5–20 percent of the U.S. population is affected by seasonal influenza. See Ctrs. for Disease Control & Prevention, Key Facts About Seasonal Influenza (Flu), <http://www.cdc.gov/flu/keyfacts.htm> (last visited Aug. 14, 2009).

⁹ Ctrs. for Disease Control & Prevention, Questions and Answers About Avian Influenza (Bird Flu) and Avian Influenza A (H5N1) Virus, <http://www.cdc.gov/flu/avian/gen-info/qa.htm> (last visited June 29, 2009).

¹⁰ Jeffrey K. Taubenberger et al., *Initial Genetic Characterization of the 1918 “Spanish” Influenza Virus*, 275 SCIENCE 1793, 1793 (1997). This mortality rate compares with the more common mortality rate of less than 0.1 percent in other influenza pandemics. *Id.*

¹¹ Richard J. Webby & Robert G. Webster, *Are We Ready for Pandemic Influenza?*, 302 SCIENCE 1519, 1519 (2003).

¹² 1 FLINT ET AL., *supra* note 3, at 511.

and C.¹³ Humans can be infected by all three, but subtype A occurs in both humans and animals, particularly in avian species.¹⁴ To date, at least 3,455 human and avian isolates have been completely sequenced.¹⁵ Influenza viruses are further classified into strains and clades, which are comprised of viruses sharing a common genetic structure.¹⁶ This organizational scheme allows epidemiologists to track the dissemination of viral strains around the world. Humans can also be infected by swine influenza strains that originate in pigs, and in fact, pigs are thought to be an ideal “mixing vessel” for multiple influenza strains.¹⁷ These facts have important implications for the spread of influenza, as some viral strains that first appear in animals can jump to humans, a host range capability that defines influenza as a potential human pathogen with an animal reservoir. Such a virus is known as a zoonotic strain, capable of crossing the species barrier.¹⁸ The clinical impact can vary across species, as an influenza virus that causes mild disease in animals may cause more severe illness in humans.¹⁹ The existence of an animal reservoir makes it unlikely that the virus can ever be completely eradicated as a potential human pathogen, in contrast to viruses such as smallpox and polio, which lack an animal reservoir.²⁰

The traditional nomenclature for clinically significant influenza viruses identifies the virus by its subtype and by two specific viral genes that mediate the infectivity of the virus: the hemagglutinin (HA) and neuraminidase (NA) genes.²¹ There are sixteen known types of HA antigens and nine known types of the NA antigens.²²

¹³ *Id.*

¹⁴ *See 2 id.* at 347.

¹⁵ Nat'l Inst. of Allergy & Infectious Diseases, The Influenza Genome Sequencing Project, <http://www3.niaid.nih.gov/research/resources/mscs/Influenza> (last visited June 29, 2009). The sequence data is available from GenBank, an international searchable online database maintained by the National Institutes of Health, National Center for Biotechnology Information, <http://www.ncbi.nlm.nih.gov> (last visited June 29, 2009).

¹⁶ Writing Comm. of the Second World Health Org. Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, *Update on Avian Influenza A (H5N1) Infection in Humans*, 358 NEW ENG. J. MED. 261, 262 (2008) [hereinafter Writing Committee].

¹⁷ OLDSTONE, *supra* note 1, at 185.

¹⁸ 1 FLINT ET AL., *supra* note 3, at 4.

¹⁹ 2 *id.* at 348.

²⁰ OLDSTONE, *supra* note 1, at 185.

²¹ Ctr. for Infectious Disease Research & Policy, Novel H1N1 Influenza (Swine Flu), <http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/index.html> (last visited July 19, 2009).

²² *Id.*

Hemagglutinin is a viral surface protein that can elicit the production of antibodies to the virus.²³ The NA protein is an enzyme on the viral membrane that facilitates the entry of influenza virus into a cell.²⁴ The dominant influenza subtypes currently circulating as seasonal strains in humans are influenza A (H1N1) (“seasonal H1N1”), influenza A (H3N2), and influenza B (which occurs only in humans).²⁵ The genome of the influenza virus changes over time, leading to the phenomena of antigenic drift (minor changes) and antigenic shift (radical changes); the latter occurs due to reassortment of the genetic segments of one or more viruses.²⁶

The possibility of human infection from an animal influenza virus means that no host immune defense may be capable of responding to and neutralizing an infection. Humans will be immunologically naïve to a viral strain with a novel HA protein and this clinical limitation can explain how an influenza virus evades host responses and causes disease.

This Article addresses the pharmaceutical interventions for an influenza pandemic in the context of patent-related biomedical research.²⁷ It presents an initial overview of the pharmaceutical options available for an influenza pandemic, followed by a description of the official U.S. and international strategies to contain a pandemic. This Article also identifies nodes where patenting could intersect with scientific research and public health planning and discusses patent-related obstacles that could impede the effectiveness of some public health efforts, as well as the strategies that might alleviate those obstacles. Much is theoretically known about the influenza virus, but the very nature of a pandemic is that a novel virus emerges that must be deciphered before a containment strategy can be devised. A chronological sequence of knowledge points can be identified that map what we must know in order to properly prepare for a pandemic: how the scientific community obtains the necessary genetic and biochemical knowledge about an emerging virus to design therapeutics; how adequate production of these agents occurs; and how the general population gets access to these treatments. Patents may sur-

²³ Writing Committee, *supra* note 16, at 263.

²⁴ 2 FLINT ET AL., *supra* note 3, at 296.

²⁵ FIORE ET AL., *supra* note 7, at 9.

²⁶ 2 FLINT ET AL., *supra* note 3, at 141.

²⁷ “Pharmaceutical interventions are the primary methods used to prevent the spread of disease as well as to reduce morbidity and mortality caused by the influenza virus.” U.S. GOV’T ACCOUNTABILITY OFFICE, INFLUENZA PANDEMIC: HHS NEEDS TO CONTINUE ITS ACTIONS AND FINALIZE GUIDANCE FOR PHARMACEUTICAL INTERVENTIONS 9 (2008), available at <http://www.gao.gov/new.items/d08671.pdf>.

face at any of these planning benchmarks, and while they may stimulate investment in research, they can also become bottlenecks to the widespread availability of knowledge or products necessary for pandemic management. Effective management of a pandemic, therefore, will turn on the development of both scientific and logistical knowledge in order to merge research insights with an appropriate legal infrastructure.

The patenting that may affect pandemic planning emerges from a nationally based intellectual property regime. A U.S. patent is a grant of rights to the first inventor that gives her “the right to exclude others from making, using, offering [to sell], or selling the invention.”²⁸ The patent term is twenty years from the date of the patent application’s filing.²⁹ Patentability turns on the satisfaction of criteria which can be conceptually divided into two groups: those that apply to the invention and those that concern the sufficiency of the patent application itself. The invention itself must satisfy the requirements for patentable subject matter,³⁰ utility,³¹ novelty,³² and nonobviousness.³³ The written patent document (the specification) must meet separate legal requirements for the adequacy of the disclosure itself.³⁴ The patent examination process that the United States Patent and Trademark Office (PTO) conducts is intended to result in the grant of patents that have met all of these requirements, and the grant therefore enjoys a presumption of validity.³⁵ Patents in other national legal regimes may be the product of similar legal requirements, but some customization occurs, although generally against the consensus requirements of the Treaty on Trade-Related Aspects of Intellectual Property (TRIPS), which launched international patent harmonization efforts in 1994.³⁶

²⁸ 35 U.S.C. § 154 (2006).

²⁹ *Id.* § 154(a)(2).

³⁰ *Id.* § 101. A patent may be granted for a process, machine, manufacture, or composition of matter. *See id.* A drug compound is a composition of matter.

³¹ *Id.* The invention must be useful, as defined by the inventor. *Id.*

³² *Id.* § 102. A patent is barred by any public disclosure of identical subject matter. *Id.*

³³ *Id.* § 103. An invention may not be patented if its subject matter would be obvious to one of ordinary skill in the art. *Id.*

³⁴ 35 U.S.C. § 112 (2006). The patent document is required to have certain attributes pertaining to the actual description of the invention, including enablement, written description, and best mode. *Id.*

³⁵ *Id.* § 282.

³⁶ General Agreement on Tariffs and Trade, Annex 1C, Agreement on Trade-Related Aspects of Intellectual Property, Apr. 15, 1994, 33 I.L.M. 1125 [hereinafter TRIPS Agreement]; *see also infra* notes 171–173 and accompanying text.

Pharmaceutical patents are a type of chemical patent, and patents may be multiply obtained for different aspects of an invention related to pharmaceutical interventions: drug compound, method of use, formulation, and production process.³⁷ Drug compound patents cover the active ingredient in the pharmaceutical product, while a method of use patent can cover the use of the product to treat a specific condition.³⁸ The potential for a pharmaceutical company to hold multiple patents related to a particular drug product can ensure a dominant position in the market. Molecular patenting in the age of biotechnology also includes the possibility of patents on viral DNA, RNA, or proteins—essentially, patents on the architectural components of the virus itself.³⁹ These attempts at patenting can be expected whenever a new microorganism appears, particularly when it is the causative agent of a clinically significant disease such as the viral strain eliciting a virulent influenza. Such patents are upstream in the research and development life cycle in the sense that they attach to the knowledge that could be essential for the development of actual downstream therapeutics. As a result, this is a potential site of patent-related obstacles to implementing the most effective responses to an identified pandemic outbreak.

Patents are inextricably linked to the research and development of pharmaceuticals in modern biomedical research.⁴⁰ Depending on the circumstances, patents may function to stimulate invention, but specific monopolistic behaviors may also limit access to the products of inventive activity. A question to be addressed is whether the predicted outlines of a pandemic health crisis generate the kind of planning that anticipates patent-related issues among the myriad legal issues that arise in pandemic management.⁴¹ Do patent-related barriers emerge in a pandemic despite careful planning by public health authorities? Can these be forecast and minimized?

Recent influenza pandemic developments have occurred across two distinct virus outbreaks. The avian influenza A (H5N1) virus, originating in Asia, has demonstrated limited spread to humans since

³⁷ JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 38–39, 44–49 (2005).

³⁸ *Id.* at 38–39, 44–45.

³⁹ See Eileen M. Kane, *DNA Patents and the Genetic Code*, 71 TENN. L. REV. 707, 712, 723 (2004).

⁴⁰ See THOMAS, *supra* note 37, at 4 (describing the consensus view that the availability of patent rights contributes to investments in pharmaceutical research).

⁴¹ Lawrence O. Gostin & Benjamin E. Berkman, *Pandemic Influenza: Ethics, Law, and the Public's Health*, 59 ADMIN. L. REV. 121, 133–34 (2007) (including intellectual property issues among the myriad legal issues relevant to influenza pandemic management).

2005, albeit with some mortality.⁴² Most official influenza pandemic planning activities and documents to date have been targeted to the possible acceleration of H5N1 to a pandemic strain capable of widespread human infection.⁴³ In April 2009, as this Article was in preparation, a novel influenza A (H1N1) (“novel H1N1”) virus was identified as the agent of an outbreak of respiratory disease that first appeared in Mexico and quickly spread to the United States and other continents.⁴⁴ This outbreak elicited a pandemic declaration from the World Health Organization (WHO), which raised its global alert to level six in June 2009.⁴⁵

Questions about the effective role of patents in the pharmaceutical field often focus on whether patents stimulate the development of new drugs and whether patents inhibit access to new and existing drugs. To these variables, the intermediate factor of capacity must be added when a health crisis involves infectious disease. Capacity concerns whether the kinetics of infectious disease might be controlled because appropriate pharmaceutical interventions have been produced and are available. Capacity precedes access. If access can be ensured, are the pharmaceuticals in ample supply for the magnitude of the health emergency? Without capacity, access will not follow. Effective management of infectious disease is a race against time, as the goal of public health authorities is not only to treat the infected but also to prevent further outbreaks.⁴⁶ Supplies and materials must therefore be ready when clinical need is identified, thus requiring advance preparation that estimates and prepares for worst-case scenarios.

⁴² See World Health Org., Cumulative Number of Confirmed Human Cases of Avian Influenza A (H5N1) Reported to WHO (Aug. 11, 2009), http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_08_11/en/index.html. The WHO reports a global total of 438 cases and 262 deaths attributable to laboratory-confirmed H5N1 in the period from 2003–2009. *Id.*

⁴³ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 1–2 (analyzing government efforts to plan for an H5N1 pandemic).

⁴⁴ Jon Cohen & Martin Enserink, *As Swine Flu Circles the Globe, Scientists Grapple with Basic Questions*, 324 SCIENCE 572, 573 (2009).

⁴⁵ Press Statement, WHO Director-General Dr. Margaret Chan, World Now at the Start of 2009 Influenza Pandemic (June 11, 2009), *available at* http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html. The alert level is an indicator of global spread of the virus, not the severity of the disease. See World Health Org., Current WHO Phase of Pandemic Alert, http://www.who.int/csr/disease/avian_influenza/phase/en/index.html (last visited Oct. 7, 2009).

⁴⁶ Gostin & Berkman, *supra* note 41, at 126.

In Part II, this Article discusses the current status of official pandemic planning for pharmaceutical interventions during an influenza pandemic. Part III identifies the patent nodes that will intersect with pandemic planning and pharmaceutical countermeasures: patents pertaining to viruses, vaccines and antivirals. Full access to these materials is critical to an effective pharmaceutical response during a pandemic. Part IV concludes with observations regarding how each of these patent nodes present different patent-related issues and how comprehensive pandemic planning can integrate intellectual property considerations in order to avoid patent-related obstacles during a public health emergency.

II. PHARMACEUTICAL INTERVENTIONS AND PANDEMIC PLANNING

The most significant pharmaceutical interventions that could be available in a viral pandemic are drawn from two distinct approaches: the administration of vaccines, which present a whole or partial virus to a potential host in order to generate an immune response that will be protective against a later infection, and the administration of antiviral medications, which are chemicals that interfere with viral replication.⁴⁷ Although these two categories of pharmaceuticals comprise the bulk of influenza-targeted research, other categories of pharmaceutical interventions exist, such as the development of monoclonal antibodies which are administered to neutralize viral infection.⁴⁸ Nonetheless, the baseline preparations for a pandemic focus on the development and stockpiling of antivirals and vaccines.⁴⁹ The loci of pandemic planning are public health authorities at the national and international level, most notably the Department of Health and Human Services (HHS) in the United States and the World Health Organization (WHO).⁵⁰

⁴⁷ U.S. GOV'T ACCOUNTABILITY OFFICE, INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC 4 (2007), available at <http://www.gao.gov/new.items/d0892.pdf>.

⁴⁸ See, e.g., Press Release, Nat'l Insts. Of Health, Researchers Find Quick Way to Make Human Monoclonal Antibodies Against Flu (Apr. 30, 2008), available at <http://www3.niaid.nih.gov/news/newsreleases/2008/humanMonoclonal.htm>; Jianhua Sui et al., *Structural and Functional Bases for Broad-Spectrum Neutralization of Avian and Human Influenza A Viruses*, 16 NATURE STRUCTURAL & MOLECULAR BIOLOGY 265, 270 (2009) (reporting the possible development of monoclonal antibodies which would neutralize many influenza A viral strains).

⁴⁹ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 9–14.

⁵⁰ See World Health Org., Pandemic Preparedness, <http://www.who.int/csr/disease/influenza/pandemic/en/> (last visited October 7, 2009); U.S. DEP'T OF HEALTH & HUMAN SERVS., HHS PANDEMIC INFLUENZA PLAN, available at <http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf>.

Active medical management of an influenza outbreak can occur at two temporal stages: 1) prevention of a possible outbreak or limiting further spread of a virulent viral strain, or 2) treatment of existing infections. Public health planning for a possible pandemic includes both strategies. Successful responses will occur against a backdrop of monitoring and surveillance by public health authorities, as they continually assess the dynamic status of an ongoing pandemic threat.

The recent outbreak of a novel H1N1 influenza occurred in the U.S. and Mexico.⁵¹ This episode displayed the sequence of knowledge that begins to appear regarding a possibly pandemic virus outbreak. The viral strain is genetically typed and assessed for its susceptibility to existing antiviral drugs. Full genetic sequencing is also necessary, as early and public dissemination of viral genetic sequences is critical to establishing global diagnostic capabilities and initiating vaccine development.

To prepare an adequate response to the newly identified virus with pharmaceutical countermeasures, pandemic planners need to determine the scientific basis for identifying the most effective vaccine and antiviral medications, locate production capabilities, and achieve stockpiling and distribution mechanisms for these pharmaceuticals. Next, this Article considers specific issues related to vaccines and antivirals.

A. Vaccines

Vaccines have been described as “the single most important pharmaceutical intervention during a pandemic.”⁵² To lead the effort to develop effective vaccines in a timely fashion, WHO has established the Global Influenza Surveillance Network (GISN), which aggregates all the national influenza centers and the four WHO Collaborating Centers into a unified mechanism for the identification of novel influenza strains and consensus decision making regarding vaccine design.⁵³ The occurrence of seasonal influenza demands that an annual vaccine composition be designed to reflect adequately the current antigenic status of the prevailing virus. The annual recommendations for the composition of the seasonal vaccine are set forth by

⁵¹ Ctrs. for Disease Control & Prevention, *Swine Influenza A (H1N1) Infection in Two Children – Southern California, March–April 2009*, 58 MORBIDITY & MORTALITY WKLY. REP. 400, 400 (Apr. 21, 2009); Cohen & Enserink, *supra* note 44, at 573.

⁵² U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 2.

⁵³ World Health Org., WHO Global Influenza Surveillance Network, <http://www.who.int/csr/disease/influenza/surveillance/en/> (last visited June 29, 2009).

GISN.⁵⁴ For example, the vaccine for the U.S. 2008–2009 influenza season was a trivalent composition composed of three circulating strains, designed to protect against the most likely sources of illness.⁵⁵

Formal pandemic planning has considered vaccine development on two fronts: a pre-pandemic vaccine, based on circulating viral strains with pandemic potential and developed before such a pandemic, and the actual pandemic vaccines, developed from the virus identified as the source of a pandemic outbreak.⁵⁶ In theory, pre-pandemic vaccine elicits some limited protective immunity and may be considered a “priming” action. The U.S. government has created a stockpile of H5N1 pre-pandemic vaccine approved by the Food and Drug Administration (FDA).⁵⁷

A vaccine—whether seasonal, pre-pandemic, or pandemic—can be composed of a virus protein, known as an antigen, such as the HA protein, or it may be composed of a whole but weakened virus. Official U.S. pandemic planning calls for the production of 600 million doses of pandemic vaccine, enough for a population of 300 million to receive two doses each.⁵⁸ A key question in vaccine design is whether antigen-sparing techniques, such as the use of adjuvants, will allow for a reduced antigenic component of the vaccine.⁵⁹

The limitation on vaccine manufacturing capabilities in the U.S. and globally represents a persistent source of concern. Several factors are responsible for this limitation. There have been technical limitations in the methods used to grow virus stock, which traditionally has relied on the use of chicken eggs.⁶⁰ With this factor and other

⁵⁴ *Id.*

⁵⁵ The U.S. vaccine against seasonal influenza is constituted of the following: Influenza A/Brisbane/59/2007 (H1N1)-like virus; an A/Brisbane/10/2007 (H3N2)-like virus; a B/Florida/4/2006-like virus. See U.S. Food & Drug Admin., Influenza Virus Vaccine for the 2008–2009 Season, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/UCM062930> (last visited June 29, 2009).

⁵⁶ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 24–25.

⁵⁷ U.S. DEP'T OF HEALTH & HUMAN SERVS., PANDEMIC PLANNING: UPDATE VI, at 2 (2009), available at <http://www.kcercoalition.com/pdf/panflureport6.pdf>. The development of a pre-pandemic vaccine can only occur for a viral strain which is identified as the source of a possible pandemic early enough to allow for development; this fact distinguishes the H5N1 situation from the ongoing A(H1N1) pandemic, which has emerged too quickly into full pandemic to allow for pre-pandemic vaccines to be developed. See Jon Cohen & Martin Enserink, *After Delays, WHO Agrees: The 2009 Pandemic Has Begun*, 324 SCIENCE 1496, 1496 (2009).

⁵⁸ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 27.

⁵⁹ *Id.* at 61; see also 2 FLINT ET AL., *supra* note 3, at 271.

⁶⁰ Catherine J. Luke & Kanata Subharao, *Vaccines for Pandemic Influenza*, 12 EMERGING INFECTIOUS DISEASES 66, 69–70 (2006).

realities of the production process, the time required to produce an effective vaccine from the time that a pandemic virus is isolated has been estimated to be four to six months.⁶¹ A further complication to vaccine production is that only a small group of companies with manufacturing capability exist.⁶² Finally, the production of a pandemic vaccine must be incorporated into the ongoing demand schedule for the production of a seasonal influenza vaccine. An initial concern in the unfolding novel H1N1 pandemic has been whether to include a pandemic vaccine component in the seasonal influenza vaccine or to instead manufacture it separately.⁶³ Both vaccines depend on the same manufacturing expertise and infrastructure.⁶⁴

The U.S. has established the Strategic National Stockpile (SNS), which is a publicly-funded repository of materials required for emergency and public health crises, including pharmaceutical supplies that are ordered and purchased from commercial manufacturers.⁶⁵ This reservoir of public health supplies exists to augment local public health efforts. Pharmaceutical supplies are distributed from the SNS within twelve hours to requesting states, and all supplies are free to the public.⁶⁶ International vaccine demand may be satisfied by the establishment of a WHO vaccine stockpile.⁶⁷

⁶¹ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 26–27.

⁶² The FDA has identified five manufacturers that are able to supply the U.S. market with influenza vaccines. U.S. Food & Drug Admin., *Influenza Virus Vaccine, Trivalent, Types A and B*, <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094045.htm> (last visited June 29, 2009).

⁶³ Although the seasonal flu virus is an H1N1 virus, it does not cross-react with the existing pandemic H1N1, so the seasonal influenza vaccine will not provide any protection against the pandemic viral strain. See Maryn McKenna, *Path to Swine Flu Vaccine Has Major Hurdles*, CIDRAP NEWS, May 1, 2009, <http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/may0109vaccine.html>.

⁶⁴ See U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 26–28.

⁶⁵ Ctrs. for Disease Control & Prevention, *Strategic National Stockpile (SNS)*, <http://www.bt.cdc.gov/stockpile> (last visited June 29, 2009).

⁶⁶ *Id.*

⁶⁷ World Health Assembly [WHA], *Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits*, at 104, Res. 60.28(2)(2) (May 23, 2007), available at http://new.paho.org/hq/images/stories/AD/HSD/CD/INFLUENZA/reso-60_28en.pdf. The resolution calls for

an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential as appropriate, for use in countries in need in a timely manner and according to sound public-health principles, with transparent rules and procedures, informed by expert guidance and evidence, for operation, prioritization, release of stocks, management and oversight.

Id.

The availability of vaccines, therefore, will depend on a combination of scientific research and logistical infrastructure. Furthermore, patents may bear on the availability of both materials and methods necessary to the vaccine development process; this will be discussed in Part III.

B. Antivirals

Antiviral drugs are molecules which have been shown to inhibit the replication of a particular virus, making them particularly suitable for administration after an individual contracts a viral infection.⁶⁸ The modern era of antibiotics is familiar to many who have been treated for bacterial infections, but viral infections represent an entirely different research challenge for scientists. Because viruses must enter the cells of an infected host in order to replicate and spread, an antiviral drug must be developed to precisely target the virus without concomitantly destroying the host cell. This is a difficult task. The Food and Drug Administration has approved several classes of antivirals for influenza outbreaks.⁶⁹ These drugs work by specifically targeting one of the viral proteins and inhibiting the ability of the virus to replicate, thereby limiting infectious spread.

One class of antivirals with effectiveness against influenza are the amantadines.⁷⁰ These drugs target the influenza A M2 protein, which is found on the internal nuclear envelope of the virus.⁷¹ Amantadine and rimantadine are the most prominent examples of this class of pharmaceuticals.⁷²

A separate class of antivirals is targeted at the neuraminidase (NA) protein of the virus, the surface enzyme that must facilitate the entry of a virus into a cell.⁷³ The NA protein is one of the two influenza proteins (along with HA) whose genetic evolution directly impacts which pharmaceutical interventions will be effective against a specific viral strain.⁷⁴ The most prominent example of the drugs that

⁶⁸ 2 FLINT ET AL., *supra* note 3, at 279.

⁶⁹ See U.S. Food & Drug Admin., Influenza (Flu) Antiviral Drugs and Related Information, <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm> (last visited Aug. 14, 2009) (“The anti-influenza antiviral drugs are not a substitute for a vaccine and are used only as an adjunct to vaccine in the control of influenza.”).

⁷⁰ 2 FLINT ET AL., *supra* note 3, at 280.

⁷¹ *Id.* at 291.

⁷² *Id.*

⁷³ *Id.* at 296.

⁷⁴ *Id.*

target NA is oseltamivir, popularly known as Tamiflu.⁷⁵ The FDA first approved the drug in 1999 and it is manufactured in capsule form by Roche, Inc.⁷⁶ A second drug in this class is zanamivir, sold under the name Relenza, manufactured and distributed by GlaxoSmithKline.⁷⁷ In contrast to Tamiflu, this drug must be inhaled.⁷⁸

The utility of preexisting antivirals in the treatment of novel viral disease is not guaranteed. A number of variables interact to make antiviral treatment uneven and ineffective.⁷⁹ The most significant complication is the emergence of antiviral-resistant strains of a virus, which have developed mutations making it possible for the virus to evade antiviral inhibition.⁸⁰ Such resistance is always a possibility in the treatment of influenza and can account for treatment failures as an influenza outbreak proceeds.

Authorities have already identified drug-resistant viral strains during the 2008–2009 seasonal influenza outbreaks.⁸¹ Such a mutation can arise as the virus evolves against a backdrop of antiviral treatment, where advantageous mutations that allow the virus to avoid antiviral inhibition will be selected for and propagated.⁸² Epidemiological reports on the 2008–2009 influenza season suggest that as many as 98 percent of the seasonal H1N1 viruses circulating in the

⁷⁵ U.S. Food & Drug Admin., Overview: Tamiflu, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=TAMIFLU&CFID=21136746&CFTOKEN=f78ab56ebccbb506-30245DD4-1143-D1C5-FB6C4048A11F8F76> (last visited June 29, 2009).

⁷⁶ *Id.*

⁷⁷ Press Release, U.S. Food & Drug Admin., FDA Approves a Second Drug for the Prevention of Influenza A and B in Adults and Children (Mar. 29, 2006), *available at* <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108622.htm>.

⁷⁸ *Compare* Relenza, Frequently Asked Questions About Relenza, <http://www.relenza.com/relenza-faqs.html> (last visited Aug. 14, 2009) (noting that Relenza is inhaled) *with* Tamiflu, Taking TAMIFLU, <http://www.tamiflu.com/taking/default.aspx> (last visited Aug. 14, 2009) (noting that Tamiflu is taken orally in pill or liquid form).

⁷⁹ 2 FLINT ET AL., *supra* note 3, at 279–81.

⁸⁰ See Ctrs. for Disease Control & Prevention, Influenza Antiviral Drug Resistance, <http://www.cdc.gov/flu/about/qa/antiviralresistance.htm> (last visited Aug. 14, 2009).

⁸¹ See Ctrs. for Disease Control & Prevention, Influenza Antiviral Resistance and Interim Recommendations for the Use of Influenza Antiviral Medications in the United States, <http://www2c.cdc.gov/podcasts/player.asp?=f10652#transcript> (last visited Nov. 5, 2009).

⁸² *Id.*

U.S. have developed a mutation in the NA gene which renders Tamiflu ineffective against the protein, resulting in drug-resistant viruses.⁸³

Antiviral-resistant viruses seriously compromise the existing portfolio of clinical responses, whether for the treatment of seasonal influenza or a pandemic influenza. If the prevailing viral agent becomes resistant to a leading antiviral, the therapeutic options diminish, and effective responses will depend on the availability of vaccines that elicit an immune response from an infected individual.

The relationship between seasonal and pandemic influenza strains is complicated; it is theoretically possible that a nascent pandemic viral strain can pick up mutations conferring drug resistance from a more benign seasonal influenza (by a reassortment process, described earlier).⁸⁴ As a result, the new virus is simultaneously virulent and less amenable to treatment. Such a phenomenon is a reminder that advance planning for antiviral responses is necessary but may be limited by the emergence of a viral strain resistant to stockpiled antivirals.

Planning for an influenza pandemic includes the stockpiling of antiviral drugs. HHS has announced its planning goal of stockpiling 75 million doses of antivirals, adequate for treatment of about 25 percent of the U.S. population.⁸⁵ These drugs are collected in the SNS and additional drugs are maintained in state stockpiles.⁸⁶

The ability to use antivirals for containment of an influenza pandemic is dependent on having adequate stockpiles of antivirals assembled and within their shelf-life range.⁸⁷ Research on the development of new antivirals for most clinically significant viruses (including influenza) continues over time. Nevertheless, pandemic preparedness is likely to rely on those drugs with an established profile in targeting influenza, most particularly the influenza subtype A that will be the likely source of any human pandemic outbreak be-

⁸³ Nila J. Dharan et al., *Infections with Oseltamivir-Resistant Influenza A(H1N1) Virus in the United States*, 301 JAMA 1034, 1034 (2009) (noting also that “influenza A[](H1N1) accounted for 19 [percent] of circulating viruses in the United States”).

⁸⁴ See *supra* note 27 and accompanying text.

⁸⁵ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 6, 54.

⁸⁶ *Id.* at 19–20.

⁸⁷ For example, manufactured Tamiflu capsules on sale in the European Union have a five-year period before expiration; recent guidance from the European Medicines Agency suggests that these capsules may be used for an additional two years, if needed, in an influenza pandemic. See Press Release, Eur. Med. Agency, European Medicines Agency Recommendations on Extension of Shelf Life for Tamiflu (May 8, 2009), available at <http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28497109en.pdf>.

cause of its animal reservoir.⁸⁸ Thus, by the time a potential pandemic is evident, effective planning will depend on antiviral capacity, not development. This shifts attention to the mechanisms for manufacture and procurement of existing drugs for the designated stockpiles. The government stockpiles will have been assembled to target critical first responders, including medical personnel, as well as selected groups of the most medically vulnerable.⁸⁹ In view of the fact that the national stockpile has only targeted capacity for 25 percent of the population, HHS also recommends that private-sector antiviral stockpiles be established for the treatment of other workers and communities not essential to the first pandemic response.⁹⁰

Patenting antiviral medications has implications for establishing full capacity in pandemic management, with further influence on actual access for individuals. This will be discussed in Part III.

III. PATENT NODES IN PANDEMIC MANAGEMENT

A. *Viruses*

The causative agent of an influenza pandemic must be determined by examining virus isolates recovered from one or more infected individuals. Viral stocks of such isolates are prepared by growing the virus in chicken eggs, the traditional method for preparing influenza virus stocks, or in cell culture, which relies on the availability of a cell line that will allow the virus to replicate.⁹¹

Isolation of the virus itself quickly leads to the goal of determining its genetic composition, namely, the RNA sequences of its genes. This research may generate potentially patentable materials, including the viral nucleic acid gene sequences, the protein amino acid sequences, recombinant vectors that host the viral genes as DNA or RNA, and cell lines which carry the viral materials.⁹² Of course, the goal of obtaining the baseline genetic structure of the pandemic virus also allows for ongoing genetic detection of variants from this original virus, an accounting of any regional variations, and a determination of the ancestry of a particular virus.

⁸⁸ See *supra* note 21 and accompanying text.

⁸⁹ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 29.

⁹⁰ *Id.* at 21.

⁹¹ Lance C. Jennings et al., *Stockpiling Prepandemic Influenza Vaccines: A New Cornerstone of Pandemic Preparedness Plans*, 8 LANCET INFECTIOUS DISEASES 650, 654 (2008).

⁹² Ben Prickril, Advisor, Pub. Interest Intellectual Prop. Advisors, Patent Landscape of H5N1 Influenza Virus at Public Interest Intellectual Property Advisors Symposium (Apr. 8, 2008), http://www.wipo.int/export/sites/www/meetings/en/2008/lifesciences/patent_landscaping/lss1_ge_08_prickril.pdf.

Public access to the genetic sequences of influenza A (H5N1) is available from several sources, all of which are dependent on the provision of virus sequences from host countries. For example, the National Center for Biotechnology Information maintains an influenza sequence database which collects the sequence data from the National Institute of Allergy & Infectious Diseases (NIAID) Influenza Genome Sequencing Project and GenBank.⁹³ An international consortium known as the Global Initiative on Sharing Avian Influenza Data (GISAID) was launched in 2006 to gather influenza sequence data, thus recognizing the need to establish consensus databases that would allow open and rapid sharing of viral sequences.⁹⁴ The guidelines for use of the database note the historical aversion to patenting by influenza virus researchers for reasons related to the nature of influenza management as well as scientific norms.⁹⁵ Nonetheless, researchers at the Centers for Disease Control and Prevention (CDC) filed a patent application advancing claims to protein sequences of the H5N1 virus in 2008.⁹⁶ In an effort to document the patent landscape of the field, the WHO has undertaken a project to map where patents have been sought on any of the relevant H5N1 viral mate-

⁹³ Yiming Bao et al., *The Influenza Virus Resource at the National Center for Biotechnology Information*, 82 J. VIROLOGY 596, 596 (2008).

⁹⁴ Peter Bogner et al., *A Global Initiative On Sharing Avian Flu Data*, 442 NATURE 981, 981 (2006).

Scientists participating in the GISAID consortium would agree to share their sequence data, to analyze the findings jointly, and to publish the results collaboratively. Data would be deposited in the three publicly available databases participating in the International Sequence Database Collaboration (EMBL, DDBJ and GenBank) as soon as possible after analysis and validation, with a maximum delay of six months.

Id.

⁹⁵ GISAID Platform, <http://platform.gisaid.org> (last visited June 29, 2009). Influenza viruses have not been subject to intellectual property rights historically. This tradition has been important because the required changes in influenza viruses contained in human influenza virus vaccines to match those viruses circulating currently in the field must occur at a speed far in excess of the legal process associated with the attainment of commercial protection. In order to allow rapid development of products such as vaccines and other interventions on an equitable basis by all countries and other interested parties, the convention has been for human health professionals to share virus specimens and data openly without creating barriers of exclusivity such as the filing of patents.

Id. Indonesia resumed supplying virus sequences to this database in 2008. *Id.*

⁹⁶ Avian Influenza Vaccine, European Patent No. WO/2008/112017 (filed Sept. 18, 2008).

rials.⁹⁷ This research demonstrates that a small cluster of patent applications have been filed on various sequences and proteins of H5N1 and several patents have been issued, but the report further notes that patent landscaping must continue as the field matures.⁹⁸ The sequence of the H5N1 and novel H1N1 influenza viruses have been determined.⁹⁹ The WHO provided notice that genetic sequences from one novel H1N1 virus isolate were available on the GISAID database within several days of the first reports of the outbreak.¹⁰⁰

Some national public health authorities are concerned that their public disclosure of regional virus isolates could lead to patents on the viral genetic sequences that will impede vaccine design or limit effective access to vaccines directed at the pandemic influenza strain. A specific controversy over the prospective patenting of influenza sequences provided to international public health agencies occurred with H5N1 in 2006, when Indonesia stopped providing virus isolates from infected individuals to international authorities.¹⁰¹ The Indonesian authorities based their action in part on the Convention on Biological Diversity (CBD), which provides that countries are entitled to benefit from the use of their genetic resources, and which the Indonesian authorities interpreted to include virus isolates from local populations.¹⁰² That interpretation, however, has been challenged.¹⁰³

The appearance of Severe Acute Respiratory Syndrome (SARS) in southern China in 2003¹⁰⁴ presented the world with a potentially

⁹⁷ Prickril, *supra* note 92, at 15–18. The project focuses on patents bearing on the actual H5N1 virus, rather than on auxiliary methods and materials. *Id.*

⁹⁸ *Id.* at 18.

⁹⁹ Rebecca J. Garten et al., *Antigenic and Genetic Characteristics of Swine-Origin 2009 (H1N1) Influenza Viruses Circulating in Humans*, 325 *SCIENCE* 197, 197 (2009); Kanta Subbarao et al., *Characterization of an Avian Influenza A (H5N1) Virus Isolated from a Child with a Fatal Respiratory Illness*, 279 *SCIENCE* 393, 394–95 (1998).

¹⁰⁰ WORLD HEALTH ORG., *VIRAL GENE SEQUENCES TO ASSIST UPDATE DIAGNOSTICS FOR SWINE INFLUENZA A(H1N1) 1–2* (2009), available at http://www.euro.who.int/Document/INF/viral_sequ_25Apr09.pdf. The WHO published the gene sequences of the viral isolate A/California/04/2009 A(H1N1). *Id.* at 2. The document listed the sequences of the major viral proteins, including the clinically important antigenic proteins, HA and NA. *Id.* at 1–2.

¹⁰¹ David P. Fidler, *Influenza Virus Samples, International Law, and Global Health Diplomacy*, 14 *EMERGING INFECTIOUS DISEASES* 88, 88–90 (2008).

¹⁰² *Id.*

¹⁰³ *Id.* at 90–92 (stating that influenza viruses are not the kind of native genetic resources contemplated by the CBD); see also Richard Holbrooke & Laurie Garrett, ‘Sovereignty’ *That Risks Global Health*, *WASH. POST*, Aug. 10, 2008, at B7.

¹⁰⁴ Ctrs. for Disease Control & Prevention, *Outbreak of Severe Acute Respiratory Syndrome – Worldwide 2003*, 52 *MORBIDITY & MORTALITY WEEKLY REP.* 226, 226 (2003). The syndrome was named by the U.S. Centers for Disease Control and a virus was suspected as the causative agent. *Id.* at 227–28.

lethal disease that was ultimately traced to a viral agent, namely, a coronavirus.¹⁰⁵ As scientists raced to identify and decipher the virus, the question of patent rights in the actual viral genes and in therapeutic pharmaceuticals complicated the coherence of an international public health strategy to contain the epidemic.¹⁰⁶ Three separate groups of international researchers filed U.S. patent applications on the DNA sequences of the virus.¹⁰⁷ The U.S. group of researchers, based at the CDC, ultimately received a patent to the DNA sequence that they identified for the virus.¹⁰⁸

In the SARS crisis, the race to identify the novel pathogenic virus was complicated by the accompanying patent-seeking on the DNA sequences for the pathogen. International public health authorities expressed concerns over the possibility that patent rights would interfere with the sharing of critical viral genetic sequences.¹⁰⁹ The WHO issued a policy statement that identified the nascent patent conflicts over the SARS virus as a potential source of concern regarding the integrity of international cooperation and patient access to clinical treatments.¹¹⁰ This WHO action served as a precursor to its later efforts to encourage the sharing of influenza H5N1 virus sequences.¹¹¹

¹⁰⁵ Matthew Rimmer, *The Race to Patent the SARS Virus: The TRIPS Agreement and Access to Essential Medicines*, 5 MELB. J. INT'L L. 335, 336 (2004).

¹⁰⁶ *Id.* at 337–39.

¹⁰⁷ *Id.* at 339–51.

¹⁰⁸ U.S. Patent No. 7,220,852 (filed April 12, 2004). “We claim 1: An isolated nucleic acid molecule consisting of the nucleotide sequences as set forth in SEQ ID NO. 1.” *Id.* The patent recites a DNA sequence of approximately 30,000 bases. *Id.*

¹⁰⁹ Rimmer, *supra* note 105, at 372–74.

¹¹⁰ World Health Org., Patent Applications for SARS Virus and Genes (Mar. 29, 2003), http://www.who.int/ethics/topics/sars_patents/en/ (last visited Nov. 5, 2009).

WHO intends to monitor the effects of patents (and patent applications) on the speed with which SARS diagnostic tests, treatments, and vaccines are developed and made available for use and on the manner in which prices are set for these technologies.

In the longer term, the manner in which SARS patent rights are pursued could have a profound effect on the willingness of researchers and public health officials to collaborate regarding future outbreaks of new infectious diseases. WHO will therefore examine whether the terms of reference for such collaborations need to be modified to ensure that the credit for any intellectual property developed is appropriately attributed, that revenues derived from licensing such property are devoted to suitable uses, and that legitimate rewards for innovative efforts do not impose undue burdens on efforts to make tests, therapies, and preventive measure available to all.

Id.

¹¹¹ WHA, *supra* note 67, at 2.

Overtones of national secrecy also shadowed the management of the SARS outbreaks; the reluctance of China to inform public health authorities of the magnitude of the crisis was severely criticized.¹¹² In hindsight, the SARS crisis demonstrates that secrecy can result from deliberate official concealment, but that the prospective patenting of critical medical information can result in effective secrecy if it retards the international sharing of virus sequences.

The SARS crisis appears to have launched recent formal efforts by the WHO to integrate patent issues into its leadership activities regarding global health. The WHO established the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property in 2008 to develop a plan for increasing the integration of patent issues into global health planning.¹¹³

The influenza viruses are both knowledge tools and physical inputs. Access to the virus and its sequence is not necessary only for vaccine design. Global monitoring of a pre-pandemic or pandemic virus is necessary for a number of reasons: to trace the ancestry of the originating virus, to conduct epidemiological surveillance, to map regional virus variations, and to identify the antiviral susceptibility or resistance of a particular virus strain. Thus, full and equitable access to influenza viruses of interest is the critical foundation for understanding and managing the scope of an influenza pandemic and for ongoing research. While patent law does not prohibit patenting isolated viruses and DNA or protein sequences *per se*, professional norms that minimize patent-seeking on influenza viruses will enhance global access to the viruses as research tools and will also remove any disincentives for public health authorities to fully cooperate in the information-sharing efforts that underlie pandemic management.

B. Vaccines

Effective vaccination of a population during an influenza pandemic awaits the identification of the causative agent necessary to construct an effective vaccine. Authorities estimate the time frame needed to design and manufacture a true pandemic vaccine to be at

¹¹² U.S. GOV'T ACCOUNTABILITY OFFICE, ASIAN SARS OUTBREAK CHALLENGED INTERNATIONAL AND NATIONAL RESPONSES 15 (2004).

¹¹³ WHA, *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, at 1–3, Res. 61.21 (May 24, 2008), available at http://apps.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf.

least five to six months from the declaration of a pandemic.¹¹⁴ Patents with potential relevance to vaccine production include patents to viral genetic sequences that are necessary for specific vaccine design, described in Part III.A, patents that pertain to specific technological processes required for the manufacture of such vaccines, patents on non-viral vaccine components, and patents on unique vaccine compositions.

Generally, vaccines that utilize the virus as an antigen can be constructed by employing either the natural reassortment process in which two or more viruses exchange segments to create a reassortant, or through reverse genetics techniques from biotechnology.¹¹⁵ In reverse genetics, the desired viral segments are built into DNA plasmids and are introduced into cells for the purpose of creating a novel virus with the designated genetic composition.¹¹⁶ Patents are held on the critical technologies of reverse genetics, including the use of several methodologies, such as the 8-plasmid system under patent to MedImmune, Inc., and the 12-plasmid system under patent to Mount Sinai Medical Center.¹¹⁷ Over the last several years, MedImmune has solidified its dominant patent position in the field of reverse genetics methods by licensing a number of patents in the field from various sources.¹¹⁸

¹¹⁴ See World Health Org., Pandemic Influenza Vaccine Manufacturing Process and Timeline, http://www.who.int/csr/disease/swineflu/notes/hIn1_vaccine_20090806/en/index.html (last visited Sept. 24, 2009).

¹¹⁵ Luke & Subharao, *supra* note 60, at 69–70.

¹¹⁶ *Id.*

¹¹⁷ David S. Fedson, *Preparing for Pandemic Vaccination: An International Policy Agenda for Vaccine Development*, 26 J. PUB. HEALTH POL'Y 19 (2005) (noting how critical vaccine method patents are to vaccine development). For an example of a critical patent on a reverse genetic method, see Helper-Free Rescue of Recombinant Negative Strand RNA Virus, U.S. Patent No. 6,649,372 (filed Nov. 28, 2000).

¹¹⁸ Press Release, MedImmune, MedImmune Expands Patent Estate for Reverse Genetics with New Rights from Mount Sinai School of Medicine (Dec. 7, 2005), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=83037&p=irol-newsArticle> (noting that the portfolio includes U.S. Patent Nos. 6,544,785 and 6,649,372).

With this license, MedImmune has further strengthened its patent estate to now either own or have exclusive licenses to all of the key intellectual property (listed below) for this technology:

Mount Sinai School of Medicine Plasmid Rescue Portfolio (WO 01/04333)

MedImmune Fundamental Reverse Genetics Portfolio (WO 91/03552)

Wisconsin Alumni Research Foundation Plasmid Rescue Portfolio (WO 00/60050)

St. Jude Children's Research Hospital Dual Promoter Plasmid Rescue Portfolio (WO 01/83794).

The actual vaccine itself is not only an output from the research and clinical processes but it may also be the subject of a patent. In addition to the possible patenting of viral genes and proteins, described in Part III.A, the use of those molecules in the creation of a vaccine with a specific pharmaceutical formulation can lead to a novel composition. Thus, the actual pharmaceutical needed to vaccinate the target population may be a patented product, as illustrated by the patents on seasonal influenza vaccines.¹¹⁹

Patents that are auxiliary to the actual viral antigen or virus may play as dominant a role in vaccine development as any actually sought on the virus components themselves. For example, the use of non-viral chemicals that augment the immunogenicity of a vaccine—known as adjuvants—is critical.¹²⁰ Such compounds allow a vaccine to include less actual antigen or virus, and thus allow for dose-sparing clinical approaches that maximize the utility of the available viral components.¹²¹ These compounds can be patented in isolation and can also appear in patents that claim a vaccine as a specific combination of antigen and adjuvant.

Patent disputes can also be avoided by advance integration of stakeholders into the patent-seeking process; such a model has occurred through the designation of joint patent ownership among academic and funding partners in the development of an AIDS vaccine.¹²² The International AIDS Vaccine Initiative has incorporated the use of access-enhancing mechanisms into the patent licensing of research that it has sponsored. Commercial licensing partners must stipulate to “access commitments” that facilitate widespread availability and agree to provide capacity levels and access.¹²³ This model

Id.

¹¹⁹ For an example, see *Influenza Hemagglutinin and Neuraminidase Variants*, U.S. Patent No. 7,504,109 (filed May 20, 2005), which was assigned to MedImmune LLC and contains product and method claims pertaining to FluMist, a seasonal vaccine manufactured by MedImmune LLC.

¹²⁰ 2 FLINT ET AL., *supra* note 3, at 271.

¹²¹ See U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 27 n.62 (noting the conservation of antigen achieved by using adjuvants in vaccine production).

¹²² *HIV Vaccines: Patents for First AIDS Vaccine Specifically Designed for Africa Will Be Jointly Owned*, AIDS WKLY., Sept. 10, 2001, at 19, 19 (noting agreement among the University of Nairobi, Kenya, the International AIDS Vaccine Initiative, and the Medical Research Council, which removed patent-mediated obstacles to the testing of a vaccine against an Africa-specific HIV virus).

¹²³ INT'L AIDS VACCINE INITIATIVE, PROMOTING INNOVATION AND ACCESS THROUGH EFFECTIVE MANAGEMENT OF INTELLECTUAL PROPERTY 2 (2007), available at http://www.iavi.org/Lists/IAVIPublications/attachments/1238/IAVI_Promoting_Innovation_and_Access_through_Effective_Management_of_Intellectual_Property_2007_ENG.pdf. “These commitments provide that any vaccine will be promptly reg-

could be followed for HHS-sponsored research aimed at designing improved methods for vaccine production.¹²⁴

There is precedent for incorporating access-enhancing mechanisms into government-funded programs that aim to combat infectious disease outbreaks. The swine flu health crisis of 1976 emerged following the appearance of a virulent in the United States.¹²⁵ An initial outbreak at the Fort Dix military base was interpreted as an initial event in a likely cascade of epidemic disease.¹²⁶ Public health experts advocated for the establishment of a national vaccine program.¹²⁷ The U.S. government recruited the leading vaccine manufacturers to the production of national stockpiles and legislation prohibited pharmaceutical manufacturers from making a profit from swine flu vaccines.¹²⁸

Unlike most pharmaceuticals, the development of a pandemic vaccine is likely to be initiated through a unique and coordinated sequence of events: public health authorities' identification of a consensus virus for vaccine development, followed by vaccine design and clinical testing, and then official purchasing by national governments from commercial manufacturers to build stockpile capacity. Thus, the development and capacity levels of vaccine resources are largely initiated and designed by public health authorities. As a corollary, access from these stockpiles is a function of official distribution, not consumer purchase. Nevertheless, patented compounds or methods required for vaccine production must be purchased or licensed by public health authorities from commercial entities who may hold patents to any of these items. The willingness to license or the licensing terms may reflect the patent-related considerations that enter the transactional evaluation. Patents could affect licensing negotiations through pricing mechanisms or limited offerings. In a public health emergency, such as an influenza pandemic, recourse to one of the patent-alleviating mechanisms available to governments is likely to ease any emergence of refusals to deal or unreasonable licensing terms. These mechanisms are discussed in Part III.D.

istered, manufactured in adequate quantities and distributed at reasonable prices in the developing world." *Id.*

¹²⁴ Press Release, U.S. Dep't of Health and Human Servs., HHS Announces Advanced Development Contract for New Way to Make Flu Vaccine (June 23, 2009), available at <http://www.hhs.gov/news/press/2009pres/06/20090623c.html>.

¹²⁵ See LAURIE GARRETT, THE COMING PLAGUE: NEWLY EMERGING DISEASES IN A WORLD OUT OF BALANCE 153-92 (1994).

¹²⁶ *Id.*

¹²⁷ *Id.* at 167-73.

¹²⁸ *Id.* at 173.

C. Antivirals

A hallmark of pandemic preparedness is the strategy of building stocks of antiviral medications for the treatment of viral infection.¹²⁹ These compounds are chosen because of demonstrable success with previous viral outbreaks.¹³⁰ A pandemic viral strain, however, is only identified after its clinical presentation; at that time, the effectiveness of existing antivirals in reducing pandemic spread will be determined.¹³¹ If viral resistance to an antiviral has developed, the antiviral stocks will not be effective and the clinical strategy of antiviral treatment may not be possible.¹³²

The leading antivirals for use in an influenza pandemic are those that target the NA protein of the virus, namely Tamiflu and Relenza, and these are the focus of stockpiling efforts.¹³³ Tamiflu (oseltamivir phosphate) was developed and patented by Gilead Sciences, Inc., a California-based biotechnology company.¹³⁴ The company then negotiated a Development and License Agreement for Tamiflu with Roche, Inc.¹³⁵ Gilead sought to terminate that agreement in 2005 due to several material breaches, including underpayment of royalties, as well as “Roche’s failure to use best efforts to commercialize Tamiflu by adequately and sustainably promoting and marketing the product in all significant markets.”¹³⁶ At the time, Gilead noted that “[e]nsuring that Tamiflu is made as widely available as possible is necessary for the protection of public health.”¹³⁷ The two companies settled after arbitration began and established a joint committee “to oversee manufacturing, commercial[,] and pandemic planning for the product.”¹³⁸ The pharmaceutical that the FDA approved has six

¹²⁹ U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 27, at 12–13.

¹³⁰ *See id.*

¹³¹ *See supra* Part II.B.

¹³² *See supra* notes 82–85 and accompanying text.

¹³³ U. S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 27, at 18, 63.

¹³⁴ U.S. Food & Drug Admin., *supra* note 75.

¹³⁵ Press Release, Gilead Sciences Inc., Gilead Delivers Termination Notice to Roche for Tamiflu Development and Licensing Agreement (June 23, 2005), *available at* http://www.gilead.ca/wt/sec/pr_723430.

¹³⁶ *Id.*

¹³⁷ *Id.*

¹³⁸ Press Release, Gilead Sciences Inc., Gilead and Roche End Tamiflu® Dispute; Expanded Collaboration Includes Gilead Role in Oversight of Manufacturing and Commercialization (Nov. 16, 2005), *available at* http://www.gilead.com/wt/sec/pr_783456.

listed U.S. patents, the latest of which expires in 2017.¹³⁹ The patent rights for Relenza (zanamivir) are licensed to GlaxoSmithKline.¹⁴⁰ The FDA-approved pharmaceutical has five listed U.S. patents, all of which expire by 2014.¹⁴¹

Effective pandemic planning requires the advance buildup of antiviral stockpiles that are available in the event of an outbreak. HHS has set a goal of keeping enough antivirals on hand for at least 25 percent of the U.S. population in the event of an influenza pandemic outbreak.¹⁴² These are kept in the SNS, which the CDC maintains.¹⁴³ States are then assigned allocations of antivirals from the national stockpile.¹⁴⁴

The chemical synthesis of antivirals requires lead time and materials. In view of the synthetic complexity of the drug, Roche has stated that it will maintain adequate levels of the chemical intermediates necessary for Tamiflu production.¹⁴⁵ The demand for private

¹³⁹ *E.g.*, Carbocyclic Compounds, U.S. Patent No. 5,763,483 (filed Dec. 27, 1996). Representative claims illustrate how a pharmaceutical patent can cover both the compound and the methods of clinical treatment:

[Claim] 1. A compound of the formula: ##STR74##. . . [Claim] 4. A method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with a compound of claim 1 or 2. . . [Claim] 6. A method for the treatment or prophylaxis of influenza infection in a host comprising administering to the host a therapeutically effective amount of a compound of claim 1 or 2.

Id.

¹⁴⁰ See Relenza, available at <http://www.biota.com.au/?page=1021002&subpage=1021104> (last visited October 7, 2009).

¹⁴¹ See, *e.g.*, Derivatives and Analogues of 2-deoxy-2,3-didehydro-N-acetyl Neuraminic Acid and Their Use as Antiviral Agents, U.S. Patent No. 5,360,817 (filed Nov. 10, 1992). Representative claims illustrate the claiming of the antiviral compound itself and its pharmaceutical formulations:

[Claim] 1. A compound of formula (Ib) ##STR22##. . . [Claim] 7. A pharmaceutical formulation comprising a compound as claimed in claim 1 as active ingredient together with a pharmaceutically acceptable carrier therefor. . . [Claim] 8. A pharmaceutical formulation suitable for intranasal administration comprising a compound as claimed in claim 1 as active ingredient together with a pharmaceutically acceptable carrier therefor.

Id.

¹⁴² U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 54.

¹⁴³ Ctrs. for Disease Control & Prevention, *supra* note 65.

¹⁴⁴ U.S. Dep't of Health & Human Servs., Antivirals—State Allocations, <http://pandemicflu.gov/professional/states/antivirals.html> (last visited Nov. 18, 2009).

¹⁴⁵ Lisa Schnirring, *Roche Cuts Tamiflu Production as Demand Cools*, CIDRAP NEWS, Apr. 26, 2007, <http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/apr2607tamiflu.html>.

stockpiling of Tamiflu also structures the production decisions of antiviral manufacturers.

The development of antiviral drugs relevant to treatment of a pandemic influenza is likely to precede any pandemic outbreak as a result of basic antiviral research, which is consistently concerned with increasing the antiviral armamentarium in medical care.¹⁴⁶ As discussed, unlike vaccines, which must be designed to target a specific causative virus, an antiviral drug can have a viral protein target which appears in many influenza strains, thus making the treatment spectrum potentially wide.¹⁴⁷ A specific influenza virus, however, may develop resistance to an existing antiviral, and this worrisome development has already emerged with the circulating seasonal H1N1 influenza strain.¹⁴⁸ If this resistance is genetically transferred to the pandemic H5N1 or novel H1N1, then Tamiflu, for example, may not be useful against one of these pandemic virus strains.¹⁴⁹ Such a clinical development could render the stockpile capacity ineffective, but cannot be predicted in advance. Stockpiles must be maintained despite the possible emergence of drug resistance.

Antiviral manufacturing can occur outside the cycles of pandemic emergence, and these drugs do enter the consumer market and are potentially available through treating physicians.¹⁵⁰ Pandemic demand, however, is likely to exceed the supplies in the baseline consumer channels,¹⁵¹ so public health authorities must consider all measures that allow antiviral reserve capacity to be established in advance.

D. Alleviation of Patent-Related Obstacles to Pharmaceutical Availability

The availability of pharmaceutical countermeasures in an influenza pandemic, whether vaccines, antivirals, or both, could potentially be constrained by the existence of the patent rights discussed in Parts III, A-C. Such complications can be anticipated and prepared for by being aware of the legal mechanisms that recognize critical circumstances where compulsory access to patented inventions for third

¹⁴⁶ Vincent Racaniello, *New Influenza Antiviral Drugs*, VIROLOGY BLOG, Jan. 28, 2009, <http://www.virology.ws/2009/01/28/new-influenza-antiviral-drugs/>.

¹⁴⁷ See *supra* notes 68–78 and accompanying text.

¹⁴⁸ See Dharan et al., *supra* note 83.

¹⁴⁹ *Id.*

¹⁵⁰ See, e.g., Tamiflu, How to Get Prescription Flu Medications, <http://www.tamiflu.com/getting/default.aspx> (last visited Oct. 7, 2009).

¹⁵¹ U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, at 7.

parties is essential for the provision of supplies in health emergencies. Recent crises involving other infectious diseases provide models for the use of such measures when necessary.

Establishing full capacity for patented antivirals, if not acceded to by voluntary licensing of relevant patents, might rely on the use of compulsory licensing measures.¹⁵² Unlike vaccines, where manufacturing capabilities are currently limited, manufacturing capability for antiviral drugs can likely be more easily accommodated by a number of pharmaceutical firms, including the roster of established generic manufacturers. The province of public health authorities will be to identify where capacity is lacking and to intercede in advance if the patent holder cannot provide adequate supplies of antivirals in a timely manner. As in all pandemic management, this is best anticipated ahead of time, due to the time lags in manufacturing and distribution that could limit the availability of treatment. Several legal mechanisms are available to make patented inventions available for use by third parties where the patent holder is unwilling or unable to supply critical products in a public health emergency. Two routes are available in U.S. patent law: the use of a compulsory license pursuant to federal statutory authority under 28 U.S.C. § 1498¹⁵³ and the use of “march-in” rights to federally funded inventions pursuant to 35 U.S.C. § 203 (Bayh-Dole Act).¹⁵⁴ On an international level, the TRIPS treaty provides flexibility for countries to invoke the compulsory licensing of patented inventions in a public health emergency.¹⁵⁵

Recent public health crises suggest these mechanisms could be effective in an influenza pandemic. The possibility of a bioterrorism-related anthrax attack appeared in the U.S. in 2001.¹⁵⁶ Anthrax is a bacterial infection, not a viral one, but the possibility that an infectious agent would spread quickly through the American population elicited a vigorous response from the government and the public

¹⁵² See BRIAN T. YEH, CONG. RESEARCH SERV., INFLUENZA ANTIVIRAL DRUGS AND PATENT LAW ISSUES 9–10 (2005), available at http://ipmall.info/hosted_resources/crs/RL33159_051118.pdf.

¹⁵³ 28 U.S.C. § 1498 (2006) gives the federal government the right to use and manufacture any patented invention, whether or not it is developed with federal funding, and can also authorize third parties to do so, subject to the payment of compensation to the patent holder.

¹⁵⁴ The Bayh-Dole Act of 1980, 35 U.S.C. §§ 200–12 (2006) allows government grantees (such as universities) to retain title to their inventions and engage in their own efforts to commercialize such technologies.

¹⁵⁵ See *infra* notes 171–173 and accompanying text.

¹⁵⁶ Martin Enserink, *This Time It Was Real: Knowledge of Anthrax Put to the Test*, 294 SCIENCE 490, 490 (2001).

health community.¹⁵⁷ Bayer, Inc., manufactured and held the relevant patents for Cipro, an antibiotic that was identified as the leading therapeutic for those exposed to anthrax.¹⁵⁸ The possibility that the U.S. government might issue a compulsory license under 28 U.S.C. § 1498 to authorize third-party manufacturing of the leading pharmaceutical was very real and represented a significant departure from existing reluctance to exercise such power.¹⁵⁹ HHS raised the specter of the compulsory license because of its concern over the price of Cipro, but did not invoke the provision.¹⁶⁰ The price of Cipro was lowered in the U.S. in response to the threat.¹⁶¹

When the threat of an H5N1 pandemic emerged in 2005, some legislators called for a compulsory license under 28 U.S.C. § 1498 to increase the manufacture of Tamiflu for the treatment of H5N1 when it appeared that Roche might not be able to satisfy demand as the sole manufacturer.¹⁶² Against this backdrop, Roche agreed to license several generic manufacturers to make Tamiflu in order to increase the stock of antivirals available in the U.S.¹⁶³

The challenge of ensuring access to antivirals during major viral illness is also illustrated by the prolonged AIDS epidemic, which arose in the early 1980s and is now responsible for a global death toll that exceeds twenty-five million.¹⁶⁴ Patented antivirals targeting HIV

¹⁵⁷ *Id.*

¹⁵⁸ Matthew Herper, *Cipro, Anthrax and the Perils of Patents*, FORBES.COM, Oct. 17, 2001, <http://www.forbes.com/2001/10/17/1017cipro.html>.

¹⁵⁹ Amy Harmon & Robert Pear, *Canada Overrides Patent for Cipro to Treat Anthrax*, N.Y. TIMES, Oct. 19, 2001, at A1.

¹⁶⁰ *Id.*

¹⁶¹ Keith Bradsher, *Bayer Halves Price for Cipro, but Rivals Offer Drugs Free*, N.Y. TIMES, Oct. 26, 2001, at A4.

¹⁶² Press Release, Senator Charles E. Schumer, As Avian Flu Closes in on U.S., Schumer Calls for Immediate Action: Demands Suspension of Tamiflu Patent So Vaccine Can Be Mass-Produced, Dramatically Increasing Supply (Oct. 16, 2005), available at http://schumer.senate.gov/new_website/record.cfm?id=260246.

¹⁶³ Press Release, Senator Charles E. Schumer, Schumer Praises Agreements with Two Major U.S. Generic Drug Companies to Increase Supply of Tamiflu to Help Stockpile Against Potential Avian Flu Pandemic (Dec. 8, 2005), available at http://schumer.senate.gov/new_website/record_print.cfm?id=260068.

Roche will continue working with these companies until the bottleneck of supply for government stockpiling purposes has been relieved, at which point they may regain their status as sole manufacturer. The purpose here is not to break the patent on Tamiflu, but rather to meet an emergency need for quantities of this drug that Roche itself simply cannot do alone.

Id.

¹⁶⁴ AVERT, Global HIV/AIDS Estimates, End of 2007, <http://www.avert.org/worldstats.htm> (last visited June 29, 2009).

(antiretrovirals known as ARVs) have been developed and effective therapeutic regimens have been established; however, there has been no express guarantee of treatment in the U.S., for example, and access has been even more irregular in poorer countries.¹⁶⁵

The challenge of ensuring access to ARVs for U.S. AIDS patients led to attempts to invoke the legal mechanism provided by the Bayh-Dole Act, the 1980 statute that allowed recipients of federal funds to seek patent protection for inventions made with these funds.¹⁶⁶ The statute allows the National Institutes of Health (NIH) to “march-in” if reasonable pricing does not occur, but the unwillingness of the NIH to employ this power has been catalogued and criticized.¹⁶⁷ In 2004, a 400 percent increase in the price of the AIDS drug Norvir, manufactured by Abbott, elicited a march-in petition to the NIH, and the NIH denied the petition.¹⁶⁸ With respect to influenza, should any relevant products or methods be determined to result from federally funded research, this authority could be petitioned for. This possibility may be more theoretical than real, however. March-in rights, having been dormant through other cycles of demand for access to pharmaceuticals, are not likely to be a fruitful means to alleviate patent-related obstacles in the future. Moreover, a pandemic crisis is likely to be addressed with government-funded antiviral stockpiles for general distribution.

HIV is a global pandemic, and controversies over access to antiviral therapeutic ARVs has implicated the patent regimes of many countries, all constructed in the shadow of TRIPS, which launched international harmonization efforts in 1994.¹⁶⁹ The treaty set up a schedule for its signatories to establish a patent regime conforming to

¹⁶⁵ See Frederick M. Abbott & Jerome H. Reichman, *The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines Under the Amended TRIPS Provisions*, 10 J. INT'L ECON. L. 921, 927 (2007) (noting divergence in the ability of developing and the least-developed countries to obtain essential medicines).

¹⁶⁶ 35 U.S.C. § 202 (2006). The Bayh-Dole Act allows government grantees, such as universities, to retain title to their inventions and to engage in their own efforts to commercialize such technologies. *Id.* § 207.

¹⁶⁷ See Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 289, 310–11 (2003) (recommending a more vigorous stance by the NIH regarding access to patented biomedical inventions made with federal funds); Anthony D. So et al., *Is Bayh-Dole Good for Developing Countries? Lessons from the U.S. Experience*, 6 PLOS BIOLOGY 2078, 2081 (2008) (noting history of unsuccessful march-in petitions).

¹⁶⁸ NAT'L INSTS. OF HEALTH, IN THE CASE OF NORVIR 1–7 (2004), available at <http://www.ott.nih.gov/policy/March-in-norvir.pdf> (NIH denial of march-in petition).

¹⁶⁹ Abbott & Reichman, *supra* note 165, at 923–27.

enacted standards, with delayed starting times for developing and the least-developed countries.¹⁷⁰ One such mechanism includes Article 31 of TRIPS, which allows the government to issue compulsory licenses for the use of patented inventions in order to serve the public interest.¹⁷¹ Although the treaty itself is a trade-motivated vehicle, it has been subject to the efforts of later ministerial conferences to enlarge the scope of TRIPS as a means of furthering other social and political goals. The most prominent example of this trend was the adoption of the Doha Declaration on the TRIPS Agreement and Public Health by the World Trade Organization Ministerial Conference in 2001.¹⁷² This document elevated attention to public health outcomes as an equally animating force for the utilization of TRIPS mechanisms.¹⁷³ Concerns over the marginalization of public health issues in the TRIPS regime persist, and there are calls to further integrate the WHO into the official apparatus of the administering authorities.¹⁷⁴

As the schedule for developing a TRIPS-compliant patent regime has been structured for slower adoption by less-developed and the least-developed countries, a number of countries with high numbers of AIDS cases have yet to offer patent rights on pharmaceutical drugs.¹⁷⁵ Several countries that have offered patent rights have encountered significant price obstacles to the availability of patented pharmaceuticals and have sought to invoke some of the flexibility of-

¹⁷⁰ *Id.* at 928.

¹⁷¹ TRIPS Agreement, *supra* note 36, at 1209, available at http://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm.

¹⁷² World Trade Organization, Ministerial Declaration of 14 November 2001, WT/MIN(01)/DEC/1, 41 I.L.M. 746 (2002) [hereinafter Doha Declaration], available at http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.htm.

We recognize that under WTO rules no country should be prevented from taking measures for the protection of human, animal or plant life or health, or of the environment at the levels it considers appropriate, subject to the requirement that they are not applied in a manner which would constitute a means of arbitrary or unjustifiable discrimination between countries where the same conditions prevail, or a disguised restriction on international trade, and are otherwise in accordance with the provisions of the WTO Agreements.

Id.

¹⁷³ *Id.*

¹⁷⁴ Kelley Lee et al., *Bridging the Divide: Global Governance of Trade and Health*, 373 LANCET 416, 420 (2009) (proposing that the WHO be officially integrated within the WTO Secretariat).

¹⁷⁵ Press Release, Int'l Centre for Trade and Sustainable Dev., TRIPS Council Agrees on Extensions for LDCs on Pharmaceutical Patents (July 3, 2002), available at <http://www.ictsd.net/i/ip/39211>.

ferred by TRIPS for public health purposes.¹⁷⁶ HIV-related patent disputes are largely responsible for testing and defining the limits of TRIPS patent-related flexibility.¹⁷⁷ Brazil issued a compulsory license for the manufacture of Efavirenz, patented by Merck, and Thailand issued a compulsory license for Kaletra, patented by Abbott.¹⁷⁸

With respect to the treatment of influenza, Taiwan invoked a compulsory license to use the Roche patent on Tamiflu under TRIPS Article 31 in 2005, as fears of a global H5N1 pandemic were spreading.¹⁷⁹ Following this action, Roche voluntarily licensed the relevant patent rights to generic manufacturers in developing countries, such as China and India.¹⁸⁰ This precedent is likely to encourage the actual or threatened use of compulsory licenses by national governments as soon as need is identified in any subsequent influenza pandemics.

Clearly, the issuance of a compulsory license to generate antiviral stockpile capacity can be invoked as a public health measure in view of the fact that post-pandemic production will not meet demand because the drug must be available at the first signs of an outbreak. Therefore, capacity cannot be the function of market forces responding only to existing medical crises or the function of stockpile capabilities established in wealthier countries. Government authorities must establish capacity either by direct purchase from the manufacturer or through other mechanisms. Antiviral drugs that are under patent in a particular country could be subject to a TRIPS-compliant compulsory license which authorizes third-party manufacturing for domestic consumption, likely at government expense.¹⁸¹

The precedents set by the HIV epidemic and the anthrax outbreak are highly relevant to the use of compulsory licenses in pandemic crisis. However, concerns over the emergence of an H5N1 pandemic in 2005 have already activated demands for the domestic

¹⁷⁶ Debate continues over the scope of TRIPS flexibility for public health purposes; this flexibility has been limited by bilateral trade treaties. See Cynthia Ho, *Current Controversies Concerning Patent Rights and Public Health in a World of International Norms*, in PATENT LAW AND THEORY: A HANDBOOK OF CONTEMPORARY RESEARCH 673, 685–95 (Toshiko Takenaka ed., 2009) (discussing the permissible scope of compulsory licenses issued under Article 31).

¹⁷⁷ See Cynthia Ho, *A New World Order for Addressing Patent Rights and Public Health*, 82 CHI.-KENT L. REV. 1469, 1484–89 (2007) (detailing the use of TRIPS-authorized legal mechanisms to ease patent-related barriers to pharmaceutical availability).

¹⁷⁸ *Id.* at 1485–88.

¹⁷⁹ Abbott & Reichman, *supra* note 165, at 948.

¹⁸⁰ *Id.*

¹⁸¹ See *supra* notes 171–173. The pending Article 31*bis* would allow a compulsory license to issue for domestic manufacturing capacity that is used to export to non-producing countries. Abbott & Reichman, *supra* note 165, at 929.

use of 28 U.S.C. § 1498, where necessary, and the actual use of the TRIPS Article 31 flexibility in Taiwan.¹⁸² These events, which grew from H5N1 pandemic concerns, will also serve as a caution for patent holders controlling future access to critical pandemic supplies, whether related to vaccines or antivirals, alerting them to incorporate public interest considerations when making decisions regarding their patented properties.

Although most examples of compulsory licensing to patented inventions during infectious disease crises have involved the provision of antiviral or antibacterial pharmaceuticals, the overarching legal principles are applicable to circumstances where materials or methods required for either vaccine or antiviral administration become limited by patent-related obstacles. Thus, public health authorities should be aware that, despite the patenting of input materials (e.g., viral genetic sequences) or output products (e.g., vaccine formulation) as well as any production or treatment methods, any unreasonable prohibitions on the availability of such patented inventions can be countered using the legal measures described above.

IV. CONCLUSION

The magnitude of a twenty-first century influenza pandemic cannot be determined with certainty; however, the outlines of containment strategies are very clear and amenable to anticipatory development in order to optimize responses. There is no shortage of government planning documents and organizations, both global and national, that can facilitate the organization and availability of personnel, supplies, and communications during a pandemic. Although most planning efforts to date have contemplated the emergence of an H5N1 influenza pandemic, public health authorities were able to rely on their broad outlines when the unexpected novel H1N1 influenza pandemic emerged earlier this year. As the world has learned from both the HIV and SARS epidemics, effective international cooperation is a necessary condition to reducing the burden of global infectious disease.

This Article has outlined how and where patenting scientific materials, technical methods, and pharmaceutical products can occur in the development of pharmaceutical countermeasures for prevention and treatment in an influenza pandemic. How do patents influence development, capacity, and access? Three key nodes of patenting emerge from the discussion: patents may control access to virus DNA

¹⁸² Abbott & Reichman, *supra* note 165, at 948.

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sequences and proteins, to vaccine production methods and actual vaccines, and to antiviral drugs that treat existing infections. A key differentiation between the impact of patents on vaccines and antivirals during an influenza pandemic emerges: patents can affect vaccine development, and subsequent capacity and access, but patents will affect antivirals only at the level of capacity and access, as their development will have occurred prior to a pandemic outbreak.

Despite the foreknowledge that pandemic planners bring to bear if confronted with a pandemic crisis, an emerging infectious outbreak will still present scientists and official authorities with a predictable set of unknowns that specifically relate to the particular microorganism responsible for the pandemic. In an influenza pandemic, the causative virus must be isolated and analyzed with allowance for any regional or population variations. The medical community will optimally want to deploy the pharmaceutical interventions of antivirals and vaccines. Several genetic realities will determine how those modalities are deployed. The pandemic viral strain must be identified and analyzed, requiring a full molecular analysis in order to generate a viral genome and specific gene sequences. Effective vaccine design requires scientific consensus regarding the virus chosen for vaccine development, followed by clinical testing to determine an immunogenic composition and a dose regimen that will provide effective immunization. The viral strain must also be tested for its susceptibility to existing antiviral agents in order to identify which antivirals should be disseminated. The possibility exists that a pandemic viral strain has resistance to one or more antivirals, in which case the range of interventions may be severely curtailed, possibly shifting the bulk of the medical response to the development of vaccines.

Patents may stimulate the development of a pharmaceutical, e.g., the research and development necessary for successful production of an antiviral drug, but the same patented antiviral may be subject to the exclusive control of its patent owner, who is able to extract maximal financial benefit from its position. In the case of pandemic planning, two realities are evident. Advance capacity of any relevant antiviral drug is required and access for infected individuals needs to be widely available in order to achieve community-wide containment of the infectious disease. A difficulty in pandemic planning is that building advance capacity will depend on government ordering and purchase, and maximal capacity will still be constrained by the ability of a patent holder to control manufacture and distribution of the drug. The 2001 anthrax crisis in the U.S. raised the specter of government exercise of its plenary right under 28 U.S.C. § 1498 to allow

third-party use of a patented invention, but this scenario unfolded during the actual public health crisis.

In an influenza pandemic, the kinetics of infectious disease and the realities of pharmaceutical production dictate several advance considerations. Building effective capacity could exceed the production capabilities or allowances of a patent holder, and the government may have to consider using a compulsory license to achieve adequate production, using third-party manufacturers and fully compensating the patent holder. But production planning must occur with knowledge of the production schedule for an antiviral drug. The actual synthetic processes can take months and thus prevent manufacture of instantaneous capacity. Therefore, pandemic planners must include patent-dictated limitations on production capacity and time constraints in pharmaceutical production when designing how adequate supplies of an antiviral drug will be procured in a relevant time period. This Article has discussed how pandemic planning requires the establishment of capacity following development in order to ensure access. One advantage of the reliance on public sector establishment of capacity is that access is then controlled by public health authorities who can distribute a drug without charge. The challenge of access, therefore, could turn on the official prioritization of access (e.g., first responders, medical personnel) rather than the usual market-mediated mechanisms that provide access as a function of price and financial ability.

If surplus manufacturing capability exists, the use of other compulsory licensing approaches is possible when considering the circumvention of patent-mediated limitations on pharmaceutical production. The theoretical use of the march-in rights afforded by the Bayh-Dole Act is a possibility for inventions resulting from the use of federal funds, even though this mechanism has not been successful to date. Furthermore, the TRIPS-structured design of national patent regimes includes the possible use of the flexibility afforded by Article 31 of the treaty, which recognizes circumstances where governments may properly invoke compulsory licenses of patented inventions in order to serve the national interest, i.e., the maintenance of public health. Such mechanisms have been used to increase access to the antiviral drugs required for treating HIV infection.

How can patent realities be recognized in pandemic planning? Consider the integration of compulsory licensing measures into the scope of legal powers that could be required in a public health emer-

gency.¹⁸³ In addition, when discussing official pandemic planning in order to ensure that vaccines and antivirals are available, consider where patented knowledge could impact pharmaceutical development and where patented products could impact availability.¹⁸⁴ For example, it is known now that patented methods for vaccine production will be required for use during a pandemic, and prospective licensing arrangements can be outlined in advance both to minimize transaction time and to determine reasonable terms. Because pandemic vaccine production essentially relies on the same infrastructure as that used for a seasonal influenza vaccine, all of the fundamental materials and methods are known in advance to pandemic planners. The crisis itself will simply supply the actual antigen or virus as the key vaccine component. Hence, patents affecting the availability of a virus protein or a whole isolated virus will be key determinants of whether a vaccine can be rapidly produced. This Article discussed why the patenting of influenza viruses may not surface as a potential barrier, but this could be due to community norms rather than any prohibition on obtaining such patents. Thus, pandemic planners must be vigilant regarding any patenting of the key viruses and their components.

There is no doubt that recent infectious diseases with global spread, such as HIV and SARS, have accelerated the coordination of international public health efforts, including the establishment of the International Health Regulations by the WHO in 2005. A further welcome development is the WHO's recent recognition of the need to integrate the management of intellectual property issues into international efforts to ensure the availability of pharmaceuticals for infectious and other diseases. Further integration would be enhanced by the increased participation of the WHO and/or public health authorities as stakeholders in discussions on the intellectual property/trade treaty interface.

The ability to offer pharmaceutical interventions for an influenza pandemic depends on three factors: development, capacity, and access. Pharmaceutical measures must be developed, capacity must be established, and access must be ensured. Patents intersect with these requirements in pandemic planning, and this Article has discussed

¹⁸³ See generally KATHLEEN S. SWENDIMAN ET AL., CONG. RESEARCH SERV., THE 2009 INFLUENZA A(H1N1) OUTBREAK: SELECTED LEGAL ISSUES (2009) (focusing only on liability and civil rights issues attendant to providing vaccines and antivirals).

¹⁸⁴ Such issues are notably absent in such U.S. planning documents and reviews. See, e.g., U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 27, (lacking any discussion of patent-related issues related to the provision of vaccines and antivirals).

where they may surface and how any obstacles may be managed. The central role of public health authorities in an influenza pandemic alters some of the traditional trajectories for the development of critical pharmaceutical interventions, but official planning must still account for the presence of patented materials and methods. As public health planners continue to deepen their awareness of the patent realities that mediate access to pharmaceuticals—a development hastened by the demands of infectious disease outbreaks—the prospects improve for a more comprehensive analysis of patents and their role in public health. Pandemic urgencies are likely to deepen the impatience with any unnecessary obstacles that patenting may pose to the provision of critical medical supplies, including pharmaceuticals. The establishment of international clinical equality during public health emergencies is essential and can provide a template for more permanent efforts to achieve health equity for all diseases.