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Influenza Antiviral Drugs and Patent Law Issues

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Summary

The potential for a worldwide influenza pandemic caused by bird flu has generated public interest in the availability and affordability of influenza antiviral medications such as the prescription drug Tamiflu. The possibility of a pandemic flu outbreak has contributed to a surge in orders for Tamiflu, as countries attempt to stockpile sufficient countermeasures. In 2005, there was considerable concern that the owner of the exclusive right to manufacture the patented drug, the Swiss pharmaceutical company Roche, Inc., lacked the production capacity to meet the needs of these governments worldwide. In response to the heightened demand for the drug, as well as faced with threatened abrogation of its patent rights by U.S. politicians and government officials in other countries, Roche significantly boosted Tamiflu production in 2006 and 2007 by voluntarily signing licensing agreements with 19 external contractors in 9 different countries to manufacture the drug. This expansion in manufacturing capacity has increased production of the drug to over 400 million treatments annually — an amount that, according to the company, is sufficient to fulfill its existing orders (as of April 2007) for Tamiflu from governments and corporations. In addition, Roche has donated "rapid response" supplies of Tamiflu (more than 5 million treatment courses) to the World Health Organization for establishing regional stockpiles to help contain or slow the spread of a pandemic. Finally, Roche has agreed to arrange for special pricing for government orders and to reduce the price of Tamiflu for low income countries.

This report examines the role that intellectual property rights play in affecting the availability of a patented drug such as Tamiflu during public health crises. The report also explains one legal mechanism for increasing a patented drug's production without the patent holder's consent: governments may abrogate a pharmaceutical company's patent rights by issuing compulsory licenses to other drug companies to manufacture generic versions of the drug. Such option is available to countries under the Trade-Related Aspects of Intellectual Property (TRIPS) Agreement, a component of the treaties that created the World Trade Organization (WTO) in 1995. The U.S. government's authority to declare compulsory licenses is Section 1498(a) of Title 28 of the U.S. Code. Other legal avenues to increase the supply of, and lower the price for, a patented drug include voluntary licensing agreements between the drug's patent holder and other companies for manufacturing or distributing the drug. In the case of Tamiflu and the avian influenza antiviral drug supply, Roche's willingness to sublicense its patent rights to several manufacturing partners has helped to lessen the concern over intellectual property rights hindering efforts to prepare for and respond to an influenza pandemic.

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Background

Avian influenza, or "bird flu," is a contagious virus that normally infects only birds but occasionally crosses the species barrier to infect humans.[1] In 1997, a particular strain of avian influenza, the H5N1 virus, infected 18 people in Hong Kong, killing 6 of them.[2] Since mid-2003, more than 258 human H5N1 cases have been diagnosed worldwide, causing more than 154 deaths.[3] According to the World Health Organization, of the few avian influenza viruses that have crossed the species barrier to infect humans, the H5N1 virus has caused the largest number of cases of severe disease and death in humans.[4]

The H5N1 virus is alarming because, if it mutates into a form that easily infects many humans, it has the potential to cause a deadly "pandemic,"[5] or a global disease outbreak in humans. In the 20th century, there were three pandemics, in 1918, 1957 and 1968, that killed millions of people worldwide.[6] On November 1, 2005, the Bush Administration issued a report entitled the "National Strategy for Pandemic Influenza," which described the federal government's plan to address the potential outbreak of avian influenza. The report explained:

> It is impossible to know whether the currently circulating H5N1 virus will cause a human pandemic. The widespread nature of H5N1 in birds and the likelihood of mutations over time raise our concerns that the virus will become transmissible between humans, with potentially catastrophic consequences. If

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[1] For more detailed information concerning avian influenza, see CRS Report RL33795, *Avian Influenza in Poultry and Wild Birds*, by Jim Monke and M. Lynne Corn.

[2] U.S. Dep't of Health and Human Services, *Avian Influenza (Bird Flu)*, at [http://www.pandemicflu.gov/general/avian.html].

[3] World Health Organization, *Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO,* November 29, 2006, *at* [http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_11_29/en/index.html].

[4] World Health Organization, *Avian Influenza Frequently Asked Questions*, at [http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html#present].

[5] An influenza pandemic "occurs when a new influenza virus emerges for which people have little or no immunity, and for which there is no vaccine. The disease spreads easily person-to-person, causes serious illness, and can sweep across the country and around the world in very short time." U.S. Dep't of Health and Human Services, *General Information About Pandemic Flu*, at [http://www.pandemicflu.gov/general/index.html].

[6] Gardiner Harris, *Bush Offers Strategy to Prepare for a Vast Flu Epidemic,* N.Y. TIMES, Nov. 2, 2005, at A20.

this does not happen with the current H5N1 strain, history suggests that a different influenza virus will emerge and result in the next pandemic.[7]

This fear of a global flu pandemic has compelled many countries to prepare for the threat by stockpiling antiviral drugs[8] and attempting to develop vaccines against the disease.[9] According to the Bush Administration, these countermeasures are "the foundation of our [influenza virus] infection control strategy."[10] The President's plan proposes to spend $1 billion to build a national reserve of antiviral medications such as Tamiflu and Relenza to help contain or suppress a pandemic outbreak.[11] As of June 2007, the nation's "Strategic National Stockpile" (SNS) contained 36 million courses of antiviral medications, with a goal of having 50 million courses anticipated to be warehoused in the federal stockpile by the end of 2008.[12] The U.S. Department of Health and Human Services (HHS) has worked with state governments to facilitate the purchase of more than 12 million treatment courses by the states as of June 2007, with a goal of obtaining 31 million courses for their respective stockpiles by December 2008.[13] HHS Secretary Michael Leavitt has explained that the "ultimate goal is to stockpile sufficient quantities of antiviral drugs to treat 25% of the U.S. population."[14] In addition to stockpiling existing antiviral drugs, the U.S. government is promoting the development of new antiviral drugs to combat

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[7] HOMELAND SECURITY COUNCIL, NATIONAL STRATEGY FOR PANDEMIC INFLUENZA (Nov. 1, 2005), at 1-2, *available at* [http://www.whitehouse.gov/homeland/nspi.pdf] (hereinafter *National Strategy*).

[8] Antiviral drugs may be used to reduce flu symptoms in persons infected with the virus, but these drugs do not provide a cure. These drugs have the potential of reducing transmission of the influenza virus or even preventing infection, under certain circumstances. DEP'T OF HEALTH AND HUMAN SERVICES, PANDEMIC PLANNING UPDATE III 9 (Nov. 13, 2006), *at* [http://www.pandemicflu.gov/plan/pdf/panflureport3.pdf]. However, some have raised concerns that the mass administration of antiviral drugs to *healthy* people for prophylactic purposes could hasten the bird flu virus developing a resistance to the drugs. World Health Organization, *Antivirals Drugs: Their Role During A Pandemic* (Nov. 2005), at [http://www.who.int/csr/disease/avian_influenza/antivirals2005_11_3/en/index.html].

[9] A vaccine is administered before humans are exposed to a disease and prevents initial infection. The U.S. Food and Drug Administration approved the first pre-pandemic H5N1 vaccine for humans in April 2007, of which the U.S. government has stockpiled 12 million doses (sufficient to treat 6 million people). This vaccine is not yet commercially available. U.S. DEP'T OF HEALTH AND HUMAN SERVICES, PANDEMIC PLANNING UPDATE IV 7 (July 18, 2007), *at* [http://www.pandemicflu.gov/plan/panflureport4.pdf].

[10] *National Strategy, supra* note 7, at 5. For more information concerning federal and state government plans to cope with pandemic influenza, *see* CRS Report RL33145, *Pandemic Influenza: Domestic Preparedness Efforts*, by Sarah A. Lister.

[11] Harris, *supra* note 6.

[12] U.S. DEP'T OF HEALTH AND HUMAN SERVICES, PANDEMIC PLANNING UPDATE IV 9 (July 18, 2007), *at* [http://www.pandemicflu.gov/plan/panflureport4.pdf].

[13] *Id.*

[14] U.S. Dep't of Health and Human Services, *HHS Assists States With Antiviral Drug Purchases,* June 30, 2006, *available at* [http://www.hhs.gov/news/press/2006pres/20060630.html].

influenza. For example, the federal government in January 2007 awarded a four-year contract of over $100 million for the development of a new influenza antiviral drug that may be quickly administered to treat persons with severe influenza.[15]

Tamiflu. Oseltamivir phosphate, marketed under the brand name Tamiflu, is a prescription drug manufactured by the Swiss pharmaceutical company Roche, Inc. Tamiflu is not a vaccine, but is perhaps the most efficient antiviral treatment for influenza.[16] The drug eases flu symptoms by preventing the influenza virus from spreading inside the human body. Some research studies have shown that Tamiflu is effective against the H5N1 avian and human virus strains.[17]

However, it is unknown how well Tamiflu would work to control a pandemic.[18] Also, the drug must be ingested within 48 hours of the onset of flu symptoms for maximum efficacy.[19] This requirement raises concerns about the utility of Tamiflu, because it is often difficult for patients to realize within such a short amount of time whether their symptoms are caused by the flu or the common cold.[20] In addition, because Tamiflu has a shelf life of five years,[21] a pandemic may not strike during that time period, raising the possibility that stockpiles of the medicine may go unused and become useless.

Prior to 2006, Roche was the exclusive manufacturer of Tamiflu and significantly struggled to meet the strong demand for the patented drug.[22] According

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[15] HOMELAND SECURITY COUNCIL, NATIONAL STRATEGY FOR PANDEMIC INFLUENZA IMPLEMENTATION PLAN: ONE YEAR SUMMARY (JULY 17, 2007), at 17, *available at* [http://www.whitehouse.gov/homeland/nspi_oneyear.pdf].

[16] Relenza, made by GlaxoSmithKline, is also an antiviral medicine, but it is more difficult to administer compared to Tamiflu because it must be inhaled. Tamiflu is given orally in capsule or liquid form. *See* Andrew Pollack, *Talk of Bird Flu Pandemic Revives Interest in Passed-Over Drugs*, N.Y. TIMES, Oct. 7, 2005, at C1.

[17] Roche, Inc., *Factsheet Tamiflu*, at 3-4, *at* [http://www.roche.com/med_mbtamiflu05e.pdf] (hereinafter *Factsheet Tamiflu*).

[18] Some strains of avian influenza virus may have developed a resistance to Tamiflu. However, scientists speculate that a Tamiflu-resistant virus would not be transmissible from person to person, and that in any event, resistant strains would not be the ones spreading in a pandemic. David Brown, *Bird Flu Virus That Is Drug-Resistant Is Found in Vietnamese Girl,* WASH. POST, Oct. 15, 2005, at A09. Roche has asserted that scientific studies do not reveal an increased resistance to Tamiflu, and point out that, to date, there have been only three documented cases of Tamiflu resistance to avian influenza H5N1. Roche, Inc., *Update on Tamiflu: No Increase in Drug Resistance Observed,* Nov. 28, 2006, *at* [http://www.roche.com/med-cor-2006-11-28].

[19] *Factsheet Tamiflu, supra* note 17, at 1.

[20] *See* Elisabeth Rosenthal, *Better Planning Is Needed for Flu Drugs, Experts Say,* N.Y. TIMES, Oct. 19, 2005, A8.

[21] Roche, Inc., *Roche Prepared to Work With Government To Supply Tamiflu, at* [http://www.rocheusa.com/newsroom/current/2005/pr2005110102.html].

[22] *See* Andrew Pollack, *Governments Pressing Roche For More of Its Flu Medicine,* N.Y.

(continued...)

to the company, manufacturing the drug is complicated, involving ten main steps, and takes a long time, from six to eight months to produce a capsule of Tamiflu once all the raw materials have been sourced.[23] In November 2005, the World Health Organization estimated that, at Roche's then-present manufacturing capacity, "it will take a decade to produce enough oseltamivir [Tamiflu] to treat 20% of the world's population."[24]

The Tamiflu production shortage in 2005 prompted both international and domestic pressures on Roche to ease its patent monopoly and permit other companies to manufacture generic versions of the drug.[25] It was believed that such action would help to increase supplies of the flu treatment to meet the backlog of orders, as well as make the drug more affordable. However, one of the challenges of producing large quantities of Tamiflu is obtaining enough supplies of its key active ingredient, shikimic acid. This acid may be extracted from the pods of a Chinese cooking spice called star anise.[26] Yet there may not be enough star anise in China or elsewhere to produce Tamiflu on a massive scale.[27] To address this shortage, Roche began experimenting with a fermentation process using genetically altered E. coli bacteria to make the shikimic acid.[28] Roche has since declared that the fermentation process is more effective in producing the acid than processing star anise, and that the majority of shikimic acid is now derived from this process.[29]

Counterfeit Tamiflu. Counterfeit drugs pose public health and safety concerns because they "may closely resemble legitimate drugs yet may contain only inactive ingredients, incorrect ingredients, improper dosages, sub-potent or

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[22] (...continued)
TIMES, Oct. 20, 2005, at C7. Sales of the once-obscure Tamiflu drug have increased from $76 million in 2001 to approximately $1.1 billion in 2005. Erica Bulman, *Tamiflu Patent: Two-Edged Sword*, SAN JOSE MERCURY NEWS, Nov. 12, 2005, at B1.

[23] *Factsheet Tamiflu*, *supra* note 17, at 4. Companies in India and Taiwan reported successfully reproducing Tamiflu in small quantities in a laboratory environment, although Roche argued that it is much more difficult and time-consuming to mass produce the drug. Nicholas Zamiska, *Generics Challenge Roche's Tamiflu Claims*, WALL ST. J., Nov. 3, 2005, at B1.

[24] World Health Organization, *Antivirals Drugs: Their Role During a Pandemic* (Nov. 2005), *at* [http://www.who.int/csr/disease/avian_influenza/antivirals2005_11_3/en/index.html].

[25] *See* Donald G. McNeil, Jr., *Indian Company to Make Generic Version of Flu Drug Tamiflu*, N.Y. TIMES, Oct. 14, 2005, at A3.

[26] Andrew Pollack, *Is Bird Flu Drug Really So Vexing? Debating the Difficulty of Tamiflu*, N.Y. TIMES, Nov. 5, 2005, at C3.

[27] *Id.*

[28] Sabin Russell, *Manufacturers Crank Out Tamiflu At a Fever Pitch,* S.F. CHRON., Nov. 10, 2005, at A4.

[29] *Factsheet Tamiflu, supra* note 17, at 4.

super-potent ingredients, or be contaminated."[30] The U.S. Federal Food and Drug Administration's Counterfeit Drug Task Force has stated:

> [W]e believe that counterfeiting is quite rare within the U.S. drug distribution system because of the extensive scheme of federal and state regulatory oversight and the steps taken by drug manufacturers, distributors, and pharmacies, to prevent counterfeit drugs from entering the system. However, we are concerned that the U.S. drug supply is increasingly vulnerable to a variety of increasingly sophisticated threats. We have witnessed an increase in counterfeiting activities and a more sophisticated ability to introduce finished dosage form counterfeits into legitimate drug distribution channels over the years.[31]

The rise in global demand for Tamiflu has contributed to the production and sale of illegal, fake Tamiflu. Pills purporting to be Tamiflu, which contain only trace elements of Tamiflu's active ingredient shikimic acid, have been shipped from parts of Asia to the United States after unsuspecting customers had ordered the counterfeit pills via the Internet; however, the U.S. Customs and Border Protection (CBP) agency has been successful in intercepting and seizing counterfeit Tamiflu shipments.[32]

Trafficking in counterfeit drugs[33] is potentially punishable under a variety of federal laws, including the mail fraud statute,[34] the Trademark Counterfeiting Act,[35] and the Federal Food, Drug, and Cosmetic Act.[36] However, prosecuting the manufacturers of counterfeit Tamiflu may prove to be challenging if they reside overseas.[37] The cooperation of foreign governments in bringing legal action against these manufacturers may be necessary to prevent the spread of fake versions of

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[30] U.S. FOOD AND DRUG ADMIN., COMBATING COUNTERFEIT DRUGS: A REPORT OF THE FOOD AND DRUG ADMINISTRATION (Feb. 2004), *available at* [http://www.fda.gov/oc/initiatives/counterfeit/report02_04.html].

[31] U.S. FOOD AND DRUG ADMIN., FDA COUNTERFEIT DRUG TASK FORCE REPORT: 2006 UPDATE (June 2006), *available at* [http://www.fda.gov/oc/initiatives/counterfeit/report6_06.html].

[32] Diana Walsh, *Customs Seizes Fake Tamiflu; Nation's First Haul of Bogus Bird Pills Traced To China,* S.F. CHRON., Dec. 19, 2005, at B1.

[33] The Federal Food, Drug and Cosmetic Act defines a "counterfeit drug" to mean a drug that, or the container or labeling of which, without authorization, bears an identifying mark of another drug manufacturer that did not manufacture the drug. 21 U.S.C. § 321(g)(2).

[34] 18 U.S.C. § 1341.

[35] 18 U.S.C. § 2320.

[36] 21 U.S.C. § 331. While counterfeit drugs are violations of intellectual property rights (potentially both patent and trademark rights), the U.S. Department of Justice prosecutes most counterfeit drug cases under the Federal Food, Drug, and Cosmetic Act. Nadine Leavitt Siak, *United States Intensifies Fight Against Counterfeit Drugs,* USINFO, Dec. 1, 2006, at [http://usinfo.state.gov/xarchives/display.html?p=washfile-english&y=2006&m=December&x=20061201120711LNkaiS0.2569086].

[37] Steve Johnson, *Bogus Bird Flu Drugs Flooding the Internet*, SAN JOSE MERCURY NEWS, Jan. 4, 2006, at 1.

Tamiflu within the global medicines market, as well as to impede their entrance into the United States.[38]

Roche has issued guidelines to help consumers avoid purchasing counterfeit Tamiflu over the Internet.[39] Among these are the following recommendations:

- Buying Tamiflu from a website exhibiting the Verified Internet Pharmacy Practice Sites (VIPPS) seal, issued by the National Association of Boards of Pharmacy after a sites's legitimacy has been confirmed.
- Avoiding Internet pharmacies that do not provide a means of contacting them by telephone
- Being wary of very low or very high prices for the drug; the average cost for authentic Tamiflu is $80 to $90 for a 10-pill treatment.
- Avoiding websites selling what they claim is "generic Tamiflu"; there is currently no authorized generic version of Tamiflu.
- Inspecting the Tamiflu package carefully for any suspicious alterations in the seal, packaging, or label. Genuine Tamiflu is packaged in a white cardboard box with the wording "TAMIFLU Capsules 75 mg" written clearly on the front. The box contains a single blister package containing 10 capsules, which are a yellow and light grey color. Each blister contains one capsule, which can be seen through the transparent outer layer. Each blister is printed on the aluminum foil of the reverse side with the words "TAMIFLU Capsules 75 mg."

Intellectual Property Issues

Patent Policy. One of the primary purposes for United States patent law is to provide individuals and institutions with economic incentives to engage in research and development that lead to new products or processes. By granting inventors with a limited monopoly[40] over the use of their discoveries, patent holders will be able to receive a return on investment from their creations. Without patent protection, competitors could "free ride" on the inventor's research and development

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[38] Carey Sargent, *Fake Drugs Are Creating Real Dangers For Consumers*, INT'L HERALD TRIBUNE, Mar. 18, 2006, at 13. *See also* Geoff Dyer, *China Busts Tamiflu Counterfeiting Ring,* FT.com, Aug. 30, 2006.

[39] Roche, Inc., *Information About Counterfeit Tamiflu, at* [http://tamiflu.com/getting/counterfeit.aspx].

[40] This time period is generally twenty years from the date of filing the patent application for most inventions. 35 U.S.C. § 154.

efforts and easily duplicate or otherwise practice the new inventions without having incurred the costs to develop them.[41]

Patent Holder Rights. A patent holder has the right to exclude others from making, using, selling, offering to sell, and importing the protected invention.[42] Whoever performs any one of these five acts during the term of the invention's patent, without authorization of the patent holder, is liable for infringement. Note that while the patent holder has the right to *exclude* others from performing these acts, the conferring of a patent does not automatically allow the invention to be used or marketed in the United States — compliance with other federal laws or regulations may be required in order to do so.[43] If a defendant is found guilty of patent infringement in a civil lawsuit brought by the patent holder,[44] the remedies available to the plaintiff include an injunction to cease and prohibit the offending activity by the defendant,[45] damages to compensate for the infringement,[46] and even attorney fees.[47]

Because the Patent Act expressly states that "patents shall have the attributes of personal property,"[48] owners may sell their patent rights in a legal transfer called an "assignment."[49] Alternatively, owners may grant others a "license" to exercise one of the five statutory patent rights A license is not a transfer of ownership of the patent, but rather is the patent owner's permission to another entity to use the invention in a limited way, typically in exchange for periodic royalty payments during the term of the patent.[50] In a licensing arrangement, legal title to the patent remains with the patent holder. If, however, the patent holder licenses to only one party the right to practice the invention within a specific territory, and the patent holder also offers that party an express or implied promise not to license the invention to any other party, then that licensee is known as an "exclusive licensee."[51]

A patent holder may grant or convey to a licensee the right to practice the invention through a contract (typically known as a patent licensing agreement). The

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[41] ROGER SCHECHTER & JOHN THOMAS, PRINCIPLES OF PATENT LAW 9-13 (2d ed. 2004).

[42] 35 U.S.C. § 271(a).

[43] For example, in the case of a patented pharmaceutical drug or medical device, the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 301 et seq., is required to review and approve such products before they may be sold to consumers.

[44] 35 U.S.C. § 281.

[45] 35 U.S.C. § 283.

[46] 35 U.S.C. § 284.

[47] 35 U.S.C. § 285.

[48] 35 U.S.C. § 261.

[49] SCHECHTER & THOMAS, *supra* note 41, at 362.

[50] *Id.* at 363-64 (citations omitted).

[51] Rite-Hite Corp. v. Kelley Co., 56 F.3d 1538, 1552 (Fed. Cir. 1995).

terms of the licensing agreement, however, may include limitations and conditions upon the grant of rights — for example, restricting the licensee from making the invention but allowing that party to sell it.[52] A patent holder may also limit the licensee to practicing the invention for a particular purpose (for example, selling a drug only to treat a particular disease) or geographic territory (for example, selling a drug only within a particular state). Generally, such restrictions are permissible, legally enforceable, and commonly found in patent licensing agreements used in many industries including the pharmaceutical industry.[53] As the U.S. Court of Appeals for the Federal Circuit[54] has previously stated:

> [P]rivate parties may contract as they choose, provided that no law is violated thereby: The rule is, with few exceptions, that any conditions which are not in their very nature illegal with regard to this kind of property, imposed by the patentee and agreed to by the licensee for the right to manufacture or use or sell the [patented] article, will be upheld by the courts.[55]

A licensee that performs an act that exceeds the scope of the license (through a violation of the limitations and conditions of the grant of rights) is potentially liable to the patent holder for breach of contract as well as for patent infringement.[56]

Tamiflu's Patent Dispute. Scientists working for a California biotech company, Gilead Sciences, Inc., invented Tamiflu in 1996. To help develop the drug for U.S. Food and Drug Administration approval[57] and its subsequent marketing and production, Gilead licensed all its commercial and manufacturing rights to Roche in exchange for a $50 million license fee[58] and royalty payments during the life of the drug's patent.[59] Tamiflu is patent-protected until 2016.[60]

In June 2005, Gilead notified Roche that it was terminating the 1996 license agreement pursuant to a clause that provides for contract cancellation due to a "material breach" of its terms. This termination would result in a reversion of

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[52] United States v. General Electric Co., 272 U.S. 476, 490 (1926).

[53] SCHECHTER & THOMAS, *supra* note 41, § 11-1.

[54] This court is a specialized tribunal that has exclusive jurisdiction to hear appeals from all district court judgments in civil actions arising under federal patent law. 28 U.S.C. §1295.

[55] Mallinckrodt, Inc. v. Medipart, Inc., 976 F.2d 700, 703 (Fed. Cir. 1992) (citing E. Bement & Sons v. National Harrow Co., 186 U.S. 70, 91 (1902)).

[56] JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 427 (BNA Books 2005).

[57] For more information concerning the FDA drug approval process, *see* CRS Report RL30989, *The U.S. Drug Approval Process: A Primer*, by Blanchard Randall IV.

[58] Sabin Russell, *Biotech Firm Wants To Regain Control of Avian Flu Drug; Gilead Says Deal with Roche Inc. Threatens Tamiflu's Production,* S.F. CHRON., Jun. 24, 2005, at A9.

[59] Nelson D. Schwartz, *The Tamiflu Tug of War,* FORTUNE, Nov. 14, 2005, at 33.

[60] *Factsheet Tamiflu*, *supra* note 17, at 2.

Tamiflu's manufacturing and commercial rights back to Gilead.[61] Gilead claimed that Roche for many years has failed to use "best efforts" to manufacture and promote the drug, and is $18 million behind in royalty payments.[62] The agreement mandates an arbitration process to resolve the dispute. On November 16, 2005, the companies announced that they had reached an amicable settlement, which amends the earlier agreement.[63] Under the terms of the settlement, Roche will reimburse Gilead $62.5 million in retroactive cost of goods adjustments, and Gilead will retain the $18.2 million that Roche had paid under protest concerning royalties owed from 2001 to 2003. However, Gilead's share of the royalties on net sales of Tamiflu will remain unchanged, ranging from 14 to 22 percent depending on the volume of sales per year. Roche and Gilead will also establish joint committees to oversee the coordination of global manufacturing and commercialization, issuing third-party licenses to generic drug makers, and pandemic planning.[64]

Patent Law and Public Health Crises. Prior to the influenza pandemic threat, two other public health crises raised patent law issues: concerns over the supply of Cipro, a drug patented by the German firm Bayer, during the anthrax bioterrorism scare in late 2001;[65] and access to affordable medication for developing countries in the 1990s to fight the HIV/AIDS epidemic in their populations.[66] Some commentators had argued for "overriding" the patent rights of the drug manufacturers in those cases, in order to allow for generic suppliers to enter the market.[67]

Those same arguments were made in the case of Tamiflu. In early October 2005, Roche repeatedly refused to license a generic version of Tamiflu.[68] The company cited the complex, time-consuming, and potentially explosive drug manufacturing process, as the reason for retaining its exclusive rights to produce

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[61] Gilead Sciences, Inc., Press Release: *Gilead Delivers Termination Notice to Roche for Tamiflu Development and Licensing Agreement,* June 23, 2005, *at* [http://www.gilead.com/wt/sec/pr_723430].

[62] *Id.*

[63] Roche, Inc., Press Release: *Roche and Gilead End Dispute on Influenza Drug Tamiflu*, Nov. 16, 2005, *at* [http://www.roche.com/med-cor-2005-11-16].

[64] *Id.*

[65] In October 2001, anthrax was sent through the U.S. mail to some members of Congress and members of the media. For more information concerning the Cipro incident and the intersection of homeland security and intellectual property law, *see* CRS Report RL32051, *Innovation and Intellectual Property Issues in Homeland Security*, by John R. Thomas.

[66] For more information regarding the issue of access to affordable medicines for developing countries, *see* CRS Report RS21609, *The WTO, Intellectual Property Rights, and the Access to Medicines Controversy*, by Ian F. Fergusson, and CRS Report RL31066, *HIV/AIDS Drugs, Patents and the TRIPS Agreement: Issues and Options*, by John R. Thomas.

[67] *See generally,* James Love, *A Better Way of Stockpiling Emergency Medicines,* FINANCIAL TIMES (London), Oct. 28, 2005, at 17.

[68] A Roche spokesperson had stated, "Roche ... fully intends to remain the sole manufacturer of Tamiflu." *See* Sabin Russell, *Flu Vaccine Maker Won't Share Patent; Roche Rejects Calls To Allow Production of Generic Versions,* S.F. CHRON., Oct. 13, 2005, at A1.

Tamiflu: "No one can do it faster. Our assumption is that it would take a generic company about three years to gear up. Therefore, it does not make sense to out-license manufacturing."[69]

This corporate position prompted criticism from domestic and international government leaders. Then-United Nations Secretary-General Kofi Annan argued that intellectual property laws should not prevent developing countries from obtaining supplies of Tamiflu and similar antiviral influenza medication in emergency health situations.[70] Senator Charles Schumer also had suggested that Congress might consider a "temporary suspension" of the Tamiflu patent if Roche did not agree to license the drug's production to other companies.[71] Other Members of the 109th Congress had expressed similar desire to abrogate Roche's patent rights in the interest of public health.[72]

Under such pressure from world leaders and politicians, Roche softened its stance and agreed to discuss sublicensing arrangements with countries and companies interested in producing generic versions of Tamiflu.[73] However, Roche has cautioned that sublicenses will only be issued to third parties that "can realistically produce substantial amounts of the medicine for emergency pandemic use, in accordance with appropriate quality specifications, safety and regulatory guidelines."[74] In 2006 and 2007, Roche expanded its capacity to manufacture Tamiflu by contracting with 19 external production partners.[75] Due to its efforts to sublicense its patent rights to manufacture Tamiflu to these other drug companies, Roche has increased production of the drug to over 400 million treatments annually (as of April 2007) — an amount that exceeds the existing orders for Tamiflu from governments and corporations.[76]

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[69] Keith Bradsher, *Pressure Rises on Producer of a Flu Drug,* N.Y. TIMES, Oct. 11, 2005, at C1.

[70] *Id.*

[71] *See* Press Release from U.S. 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," *available at* [http://schumer.senate.gov/SchumerWebsite/pressroom/press_releases/2005/PR41891.NYC%20Avian%20Flu.10.16.05.html]

[72] *See* Letter from U.S. Representative Dennis J. Kucinich, et al., to U.S. Dep't of Health and Human Services Secretary Michael Leavitt (Oct. 26, 2005), *available at* [http://kucinich.house.gov/UploadedFiles/Kucinich%20anti%20viral%20comp%20license%20request.pdf].

[73] Mark Kaufman, *Swiss Firm May Cede Bird Flu Drug Rights*, WASH. POST., Oct. 19, 2005, at A13.

[74] Roche, Inc., *Further Expansion of Tamiflu Manufacturing Capacity,* Oct. 18, 2005, *at* [http://www.roche.com/med-cor-2005-10-18].

[75] These production partners include Ampac Fine Chemicals LLC, API Corporation, Clariant, DSM, FIS, Martek, Novasep/Dynamit Nobel, PHT International, PPG Industries, Sanofi-Aventis, Shaanxi Jiahe Phytochem Co and Siegfried Ltd. *Factsheet Tamiflu, supra* note 17, at 5.

[76] Roche, Inc., *Roche Update on Tamiflu for Pandemic Influenza Preparedness*, Apr. 26, (continued...)

Legal Options

The threat of compulsory licensing (or imposing other legal limitations on Roche's patent rights) may have played a role in persuading Roche to enter into the sublicensing agreements with third parties to produce Tamiflu in greater quantities. While the concern over the then-limited supply of Tamiflu has largely been addressed by Roche's substantial manufacturing expansion, the issue of intellectual property rights potentially conflicting with public health needs may again arise in the future. Therefore, this report will now examine the ways in which a patented drug's production may be increased, either without a patent holder's consent or with the patent holder's cooperation.

The primary legal mechanisms to accomplish permissible encroachment upon a patent right include (1) compulsory licenses under a government's statutory authority to issue them; (2) compulsory licenses pursuant to an international treaty that grants this right; and (3) voluntary licensing agreements negotiated between the patent owner (or patent licensee) and third parties. This report addresses each of these options in turn.

28 U.S.C. § 1498(a). In the United States, the Takings Clause of the Fifth Amendment to the U.S. Constitution authorizes the federal government to take private property for public use.[77] Such eminent domain power over intellectual property is explicitly provided by statute, codified at 28 U.S.C. § 1498(a). This law empowers the federal government to take the intellectual property of a private entity, subject to reasonable compensation being paid to the patent holder. Section 1498(a) provides in part:

> Whenever an invention described in and covered by a patent of the United States is used or manufactured by or for the United States without license of the owner thereof or lawful right to use or manufacture the same, the owner's remedy shall be by action against the United States in the United States Court of Federal Claims for the recovery of his reasonable and entire compensation for such use and manufacture.

By exercising this statutory authority, the federal government declares a "compulsory license" that allows third-party use of a patented invention without the authorization of the patent holder. For example, if a compulsory license was issued in the case of Tamiflu, the patent holder may not enjoin generic manufacturers from producing the drug and selling it to the government for its stockpiles. The only legal remedy available to Roche would be the right to bring suit in the U.S. Court of Federal Claims to recover "reasonable and entire compensation" from the federal government. Such compensation in a patent takings case has been limited by the courts to a "reasonable royalty," which has been defined as "the amount that a person

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[76] (...continued)
2007, *at* [http://www.roche.com/med-cor-2007-04-26]. As of April 2007, Roche has received orders from governments for approximately 215 million treatments. *Id.*

[77] For more information concerning eminent domain, *see* CRS Report 97-122, *Takings Decisions of the U.S. Supreme Court: A Chronology,* by Robert Meltz.

desiring to manufacture, use, or sell a patented article, as a business proposition, would be willing to pay as royalty and yet be able to make, use, or sell the patented article, in the market, at a reasonable profit."[78]

The pharmaceutical industry warns that imposing compulsory licenses on avian flu drugs pursuant to § 1498(a) would "take away incentives for other companies to undertake the difficult and costly work of searching for new antivirals and vaccines for this possible health crisis."[79] Because drug products are time-consuming and expensive to develop but relatively easy to copy, the pharmaceutical industry is particularly dependent upon the patent system. Opponents of compulsory licensing argue that patent protection permits drug companies to benefit from their investment in research and development, and encourages them to continue to engage in such efforts. Some observers assert that "[b]reaking the patent through a compulsory license would actively discourage Roche from either producing the drug or lending its expertise, which would be directly counterproductive."[80]

At a congressional hearing on November 4, 2005, U.S. Department of Health and Human Services Secretary Michael Leavitt stated that he did not intend to issue a compulsory license for Tamiflu, because he was concerned that "violating" the patent would remove incentives for future drug research and development.[81] In another congressional hearing several days later, Secretary Leavitt stated that a compulsory license would probably not be needed in light of Roche's clear intent "not to let intellectual property issues to become a barrier" to generic manufacturing of Tamiflu, and Roche's demonstrated willingness to work with other companies to produce the drug.[82]

TRIPS and Compulsory Licenses. The Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPS Agreement") is an international agreement on intellectual property that is one component of the treaties that created the World Trade Organization (WTO) in 1995. The TRIPS Agreement establishes minimum standards of protection for patents, copyrights, trademarks, and trade secrets that each WTO signatory state must give to the intellectual property of fellow WTO members.[83] Compliance with TRIPS is a prerequisite for WTO membership.

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[78] Wang Labs., Inc. v. Toshiba Corp., 993 F.2d 858, 870 (Fed. Cir. 1993) (citations omitted).

[79] Keith Bradsher, *Pressure Rises on Producer of a Flu Drug,* N.Y. TIMES, Oct. 11, 2005, at C1.

[80] Alec Van Gelder, *Patent Nonsense on Avian Flu*, BOSTON GLOBE, Oct. 31, 2005, at A11.

[81] *The National Pandemic Influenza Preparedness and Response Plan - Is the U.S. Ready for Avian Flu?: Hearings Before the House Comm. on Gov't Reform,* 109th Cong., 1st sess. (Nov. 4, 2005) (testimony of Secretary Leavitt).

[82] *Assessing the National Pandemic Flu Preparedness Plan: Hearings Before the House Comm. on Energy and Commerce,* 109th Cong., 1st sess. (Nov. 8, 2005) (testimony of Secretary Leavitt).

[83] World Trade Organization, Understanding the WTO - Intellectual Property: Protection and Enforcement, *at* [http://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm].

Article 31 of the TRIPS Agreement addresses the right of WTO member states to award compulsory licenses. This article specifies a number of procedural and substantive conditions for issuing compulsory licenses, including the following:[84]

- Domestic law must permit compulsory licenses to be granted.
- Manufacturing of a patented invention under a compulsory license shall be predominantly for the supply of the domestic market of the WTO member state authorizing such use.
- Authorization for such use must be terminated if and when the compulsory license's motivating circumstances cease to exist and are unlikely to recur.
- The patent owner must be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization.
- Under normal circumstances, the proposed user must have tried to obtain permission from the patent holder on reasonable commercial terms and conditions. If these efforts fail to obtain a voluntary license, the government may issue a compulsory license.

Notably, Article 31 does not discuss the circumstances under which compulsory licenses would be justified.[85] However, for "national emergencies" and "other circumstances of extreme urgency," Article 31 provides that a compulsory license may issue without the proposed user having to first make an effort to obtain a voluntary license from the patent holder.[86] This time-saving, "national emergency" provision in TRIPS was clarified by the WTO in November 2001 and again in August 2003. The November 14, 2001 "Declaration on the TRIPS Agreement and Public Health" (Doha Declaration) affirms that the TRIPS Agreement "can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all."[87] In addition, the Doha Declaration explains that each WTO member state "has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those

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[84] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, art. 31, 33 I.L.M. 1197, 1209-10 (1994).

[85] *See* World Trade Organization, *Declaration on the TRIPS Agreement and Public Health,* para. 5b, WT/MIN(01)/DEC/2 (adopted Nov. 20, 2001), *available at* [http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm] ("Each member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.").

[86] World Trade Organization, *Compulsory Licensing of Pharmaceuticals and TRIPS, at* [http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm].

[87] *Id.* at para. 4.

relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency."[88]

Confronted with these public health emergencies, WTO members with insufficient or no manufacturing capacities in the pharmaceutical sector may be unable to make effective use of compulsory licensing under the TRIPS Agreement.[89] The WTO's proposed solution to this problem was announced on August 30, 2003, when the WTO General Council issued a decision that allows member states, meeting certain strict conditions, to import generic versions of drugs produced under compulsory licenses issued by other countries. Specifically, this "Paragraph 6 Agreement" permits a waiver of Article 31(f) of the TRIPS Agreement, which specifies that compulsory licenses are to be used predominantly for the supply of the domestic market.[90] Thus, countries that produce generic drugs under a compulsory license may export them to other WTO members that are unable to manufacture the medicine to meet their urgent needs.

As many nations attempt to stockpile antiviral drugs to prepare for the possible bird flu pandemic, the TRIPS "national emergency" provision for compulsory licenses has garnered public interest as a possible way to increase the production and supply of Tamiflu.[91] However, at the time of the Paragraph 6 Agreement, the United States and 22 other developed countries decided to "opt-out" of using the compulsory license system as importers, under any and all circumstances.[92] Some observers have speculated that the reason for this decision is to discourage compulsory licensing and put pressure on developing countries not to use it.[93] An official in the Office of the U.S. Trade Representative has explained, however:

> In the negotiations leading up to this solution, developed nations as a whole recognized that it was not appropriate for us to import pharmaceuticals under this

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[88] *Id.,* at para. 5c.

[89] *Id.,* at para. 6.

[90] World Trade Organization, *Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health,* WT/L/540 (Aug. 30, 2003), available at [http://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm]. On December 6, 2005, the WTO General Council agreed to make the August 2003 "waiver" a permanent amendment to the TRIPS Agreement. At least two-thirds of the membership of the WTO must ratify the amendment by December 1, 2007, for the amendment to go into effect for those WTO Members that adopt it. The United States formally adopted the amendment on December 17, 2005. World Health Organization, *Members OK Amendment to Make Health Flexibility Permanent,* Dec. 6, 2005, *at* [http://www.wto.org/english/news_e/pres05_e/pr426_e.htm].

[91] Uta Harnischfeger, *Groups Want WTO Rules Eased Over Bird Flu*, Associated Press Financial Wire, Oct. 25, 2005, *available at* [http://www.iatp.org/tradeobservatory/headlines.cfm?refID=77225].

[92] Statement of General Council Chairperson, WT/GC/M/82 (Nov. 13, 2003), (excerpt from the minutes of the General Council meeting of Aug. 30, 2003), *available at* [http://www.wto.org/english/tratop_e/trips_e/gc_stat_30aug03_e.htm].

[93] James Love, *What Bush Did Not Explain About Bird Flu*, Nov. 1, 2005, *available at* [http://www.huffingtonpost.com/james-love/what-bush-did-not-explain_b_9968.html].

> system devised to assist poor countries and agreed not to divert attention and resources away from countries the system was intended to benefit. It was also apparent that the United States was not a country that lacked manufacturing capacity, given our robust pharmaceutical manufacturing base and the prevalence of thriving U.S. innovative and generic pharmaceutical industries.[94]

Yet this opt-out may effectively prevent developed countries from importing generic versions of Tamiflu made by companies in countries that exercise Article 31 compulsory license authority or in which Tamiflu is not patent-protected.[95] In late 2005, with Roche's production capacity limitations affecting the ability of countries to procure enough Tamiflu to treat their populations, the United States' decision to opt-out had become the focus of criticism and appeal for change.[96] A bill was introduced in the 109th Congress that would have directed the U.S. Trade Representative to notify the WTO General Council that the U.S. declares itself an "eligible importing member" for Paragraph 6 purposes, and that it withdraws its name from the opt-out list of countries.[97] However, in a congressional hearing on November 8, 2005, U.S. Department of Health and Human Services Secretary Michael Leavitt downplayed the consequences of the opt-out decision, arguing that in a global pandemic situation, each country will likely only have access to what it produces domestically, as countries will want to keep domestically-produced flu drugs inside their own borders.[98]

Licensing Agreements. If Tamiflu was subject to a compulsory license, Roche would still be entitled to receive three to five percent royalties. However, Roche would have no ability to control the sale price of the drug, and a cheaper generic version would mean smaller royalty payments.[99] Roche thus would prefer an

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[94] Letter from Victoria Espinel, Victoria Espinel, Acting Assistant United States Trade Representative for Intellectual Property, to James Love, *available at* [http://www.cptech.org/ip/health/tamiflu/ustr02092006.pdf].

[95] *See* Letter from James Love to U.S. Trade Representative Rob Portman (Oct. 14, 2005), *available at* [http://www.cptech.org/ip/birdflu/ustr-birdflu.html]. Tamiflu is not patent-protected in several countries, including Thailand, the Philippines, and Indonesia. *Factsheet Tamiflu, supra* note 17, at 6.

[96] Letter from James Love to U.S. Trade Representative Rob Portman (Oct. 14, 2005), *available at* [http://www.cptech.org/ip/birdflu/ustr-birdflu.html]*; see also* Statement of Consumers International to TRIPS Council (Oct. 25, 2005), *available at* [http://www.cptech.org/ip/health/tamiflu/ci10252005.html].

[97] H.R. 4392, 109th Cong., 1st sess. (2005), was introduced by Representative Thomas H. Allen on November 18, 2005, and referred the same day to the House Committee on Ways and Means. No further action was taken on the bill before the adjournment of the 109th Congress.

[98] *Assessing the National Pandemic Flu Preparedness Plan: Hearings Before the House Comm. on Energy and Commerce,* 109th Cong., 1st sess. (Nov. 8, 2005) (testimony of Secretary Leavitt).

[99] Erica Bulman, *Tamiflu Patent: Two-Edged Sword,* SAN JOSE MERCURY NEWS, Nov. 12, 2005, at B1.

alternative to the use of compulsory licensing, which are licensing agreements voluntarily negotiated by the company with third-parties of its choosing.[100]

Licensing agreements are contracts between the patent owner (or patent licensee) and third parties that may be used to permit third parties to exercise one of the rights of the patent owner or patent licensee (in the case of a patent licensee, the contract is known as a sublicensing agreement). For example, Roche (a licensee of the patent owner Gilead) may permit other companies to manufacture and market Tamiflu in exchange for the companies paying licensing fees to Roche and agreeing to certain conditions. Such conditions in the sublicensing agreement may restrict the sale of Tamiflu to emergency government stockpiles, prevent re-exports of the drug, and time-limit the sublicense.[101] An advantage of a sublicensing scheme is that the other pharmaceutical companies can seek and obtain Roche's manufacturing expertise to ensure quality production.[102] In addition, sublicensing allows for coordination of obtaining the active ingredient in the antiviral drug, shikimic acid.[103] However, some critics have asserted that these voluntary sublicensing agreements might only help rich countries to stockpile Tamiflu, and do little to improve the treatment's availability for poorer countries.[104] They maintain that under such agreements, Roche would likely still retain the right to control pricing and could reap large profits on generic Tamiflu.

As of April 2007, Roche has signed sublicensing agreements with 19 contractors to manufacture Tamiflu in nine different countries around the world.[105] In addition, Roche has donated "rapid response" supplies of Tamiflu (more than 5 million treatment courses) to the World Health Organization for establishing regional stockpiles to help contain or slow the spread of a pandemic. Finally, Roche has agreed to arrange for special pricing for government orders and to reduce the price of Tamiflu for low income countries.[106]

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[100] Roche, Inc., *Roche Announces Further Progress in Tamiflu Production Expansion,* Nov. 7, 2005 (stating that Roche is willing to "negotiate with any partner about granting a license [for Tamiflu] at equitable conditions.... Selection criteria are quality, technical ability, capacity and the speed of bringing that capacity on stream."), *at* [http://www.roche.com/med-cor-2005-11-07].

[101] James Kanter, *Roche Offers To Negotiate on Flu Drug,* N.Y. TIMES, Oct. 19, 2005, at C1.

[102] *A Patent Solution: Bird Flu Revives the Trickiest Questions in Intellectual Property*, FINANCIAL TIMES (London), Oct. 21, 2005, at 18.

[103] See discussion of shikimic acid, *supra* page 4.

[104] Brook K. Baker, *Roche's Secret, Sub-Licenses for Tamiflu Will Not Bring Poor People in From the Cold,* available at [http://www.health-now.org/site/article.php?menuId=12&articleId=504].

[105] Roche, Inc., *Roche Update on Tamiflu for Pandemic Influenza Preparedness*, Apr. 26, 2007, *at* [http://www.roche.com/med-cor-2007-04-26].

[106] *Id.*

Conclusion

Should the H5N1 virus, or some other avian influenza strain, cause a human pandemic, antiviral drugs will likely play a critical role to help prevent infection and to relieve the flu symptoms of those infected. The Tamiflu supply shortage in 2005 had sparked public debate concerning the practicality and morality of protecting intellectual property rights during a possible health crisis, which can directly affect the availability and affordability of medicine for populations in dire need of it. However, because Roche has since reached sublicensing agreements with several manufacturing partners that have significantly increased production of Tamiflu to satisfy global demand for the drug, the concern about intellectual property rights hindering preparations for pandemic influenza has largely subsided. crsphpgw

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