IP Rumble in China:

Tony Chen on remdesivir patents controversy

The rush to uncover potential therapies against the novel coronavirus (SARS-nCoV-2) and its associated pneumonia, COVID-19, recently brought intellectual property (IP) protection issues in the Chinese pharmaceutical market into sharp focus. Gilead Sciences' broad-spectrum antiviral candidate remdesivir was quickly identified as among the few drugs with potential efficacy against COVID-19. However, Gilead's control over the drug in China was undermined by a wildcat patent filing from the Wuhan Institute of Virology that had helped to uncover its potential. This was followed by three listed domestic pharmaceutical companies issuing public statements claiming to have established the ability to manufacture remdesivir. GBI spoke with Jones Day partner Tony Chen for his view on recent events, the nature of the risk, and implications in light of China's recently signed US-China Phase One Trade Deal.

Wuhan Institute swoops

Remdesivir was one of seven drugs screened by a team of Chinese researchers at the Wuhan Institute of Virology (WIV), part of the Chinese Academy of Sciences (CAS), for potential efficacy against COVID-19 as soon as the SARS-nCoV-2 outbreak occurred in December 2019. Gilead's experimental drug candidate emerged as the strongest of the seven based on ability to inhibit the virus in cell lines, and researchers advised immediate tests in the clinic.

On February 4, 2020, the same day that those drug screening results were published in Cell Research,[1] WIV revealed in a notification on its website that it had filed a patent application in China on January 21, 2020, covering

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Tony was trained as a molecular biologist before studying law at Harvard University. He practiced patent law in California for more than a decade where he represented a wide range of high-tech and biotech companies. He also acted as an in-house patent counsel for a leading specialty pharmaceutical company. In addition, he co-founded a drug discovery technology company in Silicon Valley. Since moving to China in 2004, Tony has represented multinational companies to enforce their intellectual property rights in civil and criminal actions and to assist them in reducing IP risks in R&D activities in China. He has also represented Chinese companies to build and procure intellectual property on a worldwide basis. He has advised Shanghai and Suzhou technology parks on life science industry and intellectual property matters.

remdesivir's use specifically for the indication of COVID-19, and was also filing via the Patent Cooperation Treaty (PCT) "in accordance with international practice". WIV stated that it was acting "from the perspective of protecting the national interest" during the epidemic, with the proviso that, "If affected foreign companies are willing to contribute to the prevention and control of China's epidemic, we agree in the interests of the nation we will not require the implementation of the rights claimed by the patent at present, and hope to work with the affected foreign pharmaceutical company, to the extent that both sides are in agreement, to contribute to the prevention and control of the disease outbreak" (GBI translation). [2]

WIV's exact patent claims will not be made public for 18 months, as per standard practice for PCT filings. Tony Chen explained the legal basis for WIV's filing, despite not being the inventor of remdesivir: "When a compound structure is public, people can get hold of that and start to do experiments, and if you are the first one to find out that a particular drug can be used to treat a certain disease not covered in the previous disclosure, then you can file a patent application for the method of use for that indication. You can file, and you deserve a patent [...] so long as what you're seeking is new and inventive".

In terms of WIV's ultimate aim, Chen noted that should a patent be awarded to WIV for remdesivir's use against COVID-19 it could force a cross-license arrangement. This would mean that Gilead, despite being the original license holder, would need "a license from the Institute to sell the drugs for treating COVID-19". "In that case, the Wuhan Institute could approach Gilead and say, I want you to give me a license in return for my giving you a license", a form of cross-licensing that Chen notes is common within the electronics industry.

Question marks around Gilead's patent awards

The prospect that a promising life-saving COVID-19 drug candidate could be "hijacked" by fast-moving Chinese researchers provoked consternation among multinational corporations (MNCs) operating in China. The government apparently sought to address the issue when He Zhimin, the deputy-director of the China National Intellectual Property Administration (CNIPA; formerly State Intellectual Property Office; SIPO), was quoted by local media in late February as stating that Gilead's molecule had already been awarded three patents in China, with another five still under consideration.

Chen noted that two of Gilead's remdesivir patents were awarded prior to the COVID-19 outbreak, while no details regarding a third patent have been made public: "If they say they have granted three Chinese patents then let us see all three of them". The questions raised by WIV's filing are also not resolved by He Zhimin's statement, said Chen: "No matter how many patents the Chinese patent office has granted to Gilead, it does not tell you whether they will grant or deny a patent to the Wuhan Institute of Virology. That is a separate issue".

Listed domestic firms censured over 'newsjacking'

While the patent controversy surrounding remdesivir rumbled on, further challenges to Gilead's commercial prospects for the molecule arose. Three domestic pharmaceutical companies issued public claims to have established manufacturing capabilities in regard to remdesivir:

• On February 12, BrightGene Bio-Medical Technology issued a statement claiming to have established the ability to synthesize remdesivir API and formulated product, and to be preparing to begin manufacturing a 'batch' of the drug.

• On February 13, Materials Industry Zhongda Group, communicating with shareholders via their interactive e-platform, indicated that local government approval had been awarded to set up a production plant capable of manufacturing 10 million tablets of remdesivir each year. Zhongda also issued a public risk alert to investors regarding the earlier statements.

• On February 15, Hainan Haiyao released a stock exchange announcement stating that it had established the capability to manufacture remdesivir API and up to 3.5 million tablets of formulated product each year.

All three companies acknowledged that they did not have license to Gilead's patents. Two of the firms (BrightGene and Zhongda Group) were subsequently reprimanded by China's Securities and Exchange Commission (SEC) for misleading the public.

Because the three companies are not conducting remdesivir clinical trials in China, Chen says the three companies' public statements read like an admission of patent infringement: "They have manufactured the API, produced formulated drug, plan to produce large quantities, and want to sell. Don't they know the patent law says that you shall not make, use, sell, or offer to sell [patented products] without patentee's authorization?".

In Chen's view, the episode is indicative of the "no worries about patents" climate in China's pharmaceutical industry after a string

1. https://www.nature.com/articles/s41422-020-0282-0
2. 我国学者在抗 2019 新型冠状病毒药物筛选方面取得重要进展； http://www.whiov.cas.cn/kyjz_105338/202002/t20200204_5497136.html
3. 物产中大蹭瑞德西韦热点 公司及董秘陈海滨被通报批评； http://stock.jrj.com.cn/2020/03/02112628933495.shtml]

Table 1. Recent first-time generic drug approvals in China versus Orange Book listed originator patent expiries

Molecule name / Brand	Formulation / dosage	Originator	Orange Book patent expiry*	Patent type	First mover generic	Generic approval date
Imatinib / Gleevec	Capsule / 0.1g	Novartis	2021-10-26	Indication	Jiangsu Hansoh Pharmaceutical	2018-05-31
Moxifloxacin / Avelox	Tablet / 0.4g	Bayer AG	2019-10-29	Formulation	Guangdong Dongyangguang Pharmaceutical	2018-07-06
Ticagrelor / Brilinta	Tablet / 60mg and 90mg	AstraZeneca	2019-12-02	Compound	Shenzhen Salubris Pharmaceuticals	2018-07-31
Apixaban / Eliquis	Tablet / 2.5mg	Bristol-Myers Squibb	2022-09-17	Compound	Jiangsu Hansoh Pharmaceutical	2019-01-09
Saxagliptin / Onglyza	Tablet / 5mg	AstraZeneca	2021-03-05; 2025-05-26; 2025-05-26	Compound	Jiangsu Aosaikang Pharmaceutical	2019-01-09
Vildagliptin / Galvus	Tablet / 50mg	Novartis	2019-12-09; 2025-01-17	Compound; Product / formulation	Jiangsu Hansoh Pharmaceutical	2019-03-06
Rivaroxaban / Xarelto	Tablet / 10, 15 and 20mg	Bayer AG	2020-12-11; 2024-11-13	Compound; Product / formulation	Chia Tai Tianqing Pharmaceutical	2019-08-02
Anastrozole / Arimidex	Tablet / 1mg	AstraZeneca	2022-12-06	Indication	Zhejiang Hisun Pharmaceutical	2019-10-28
Sunitinib / Sutent	Capsule /12.5mg	Pfizer	2021-02-15	Product / compound	CSPC Ouyi Pharma	2019-12-26
Sitagliptin / Januvia	Tablet / 100mg	Merck Sharp & Dohme	2022-07-05; 2024-06-18	Compound; product / compound salt	Chia Tai Tianqing Pharmaceutical	2020-02-25

**Patent expiry dates are extrapolated from China Orange Book drug listing details (http://list.cde.org.cn/index/lists)*

Source: GBI SOURCE

of well publicized NMPA approvals issued for generic drugs in 2019 before expiration of innovators' Chinese patents. In September 2020, a new draft of the Drug Registration Regulation (DRR) released for public feedback removed a clause requiring the National Medical Products Administration (NMPA) to wait for patent expiry before approving generic drugs (Article 19 of the existing DRR). The NMPA began applying that change without the DRR's formal implementation, with several key generics recently given market nods while still covered by patents listed in the China Orange Book (see Table 1). "You can see that generic drug companies have drawn a moral lesson from these examples", noted Chen. On March 30, the NMPA formally promulgated the revised DRR, which will take effect on July 1, 2020.

Compulsory license risk

In responding to the SEC reprimand, Materials Industry Zhongda's board secretary Chen Haibin justified the company's lack of consideration for Gilead's patents by citing the likelihood of a compulsory license being issued to one or more pharmaceutical companies in relation to remdesivir. [3]

Compulsory licensing allows governments to order manufacturing of a patented product be transferred to a generic firm without the consent of the patent owner, typically due to national public health threats. The measure has been a legal possibility in China since the country signed up to the World Trade Organization (WTO)'s TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement in 2000, although relevant provisions were not written into the Patent Law until 2008. SIPO made further adjustments to those terms in 2012.

Although a compulsory license has never been granted in China, there are examples of its latent threat leading to concessions from originator companies. In 2005, amid rising cases of avian influenza around the world, Roche decided to preempt any move towards compulsory licensing by handing out manufacturing rights to Tamiflu (oseltamivir) to 12 companies

in different markets, including generic drug companies in China. In the following year, the CFDA then issued two further market approvals to Shanghai Sunve Pharmaceuticals and Yichang Changjiang Pharmaceutical for the drug.

Chen highlighted a feature of China's compulsory license rules that would allow China based generic drug companies to supply remdesivir to other countries afflicted by COVID-19: "A Chinese company could apply for a compulsory license for generic remdesivir produced in China to be exported" (see Insert below), especially to countries that might not recognize Gilead's remdesivir patent or be deemed as "underdeveloped" markets under the terms of China's compulsory licensing laws.

Insert: China's compulsory licensing terms

China's Patent Law permits compulsory licenses to be issued under five different scenarios:

- **Insufficient patent exploitation:** Patentee fails to fully or sufficiently implement the patent right for a certain period of time (drug companies apply)

- **Monopoly:** Exercise act of patentee is deemed a monopolistic act (drug companies apply)

- **Public emergency:** In a state of emergency, or when serving the public interest (at government discretion)

- **Public health exports**: For public health reasons, compulsory license can be granted against patented medicines in order to produce/export outside China to "underdeveloped countries" (drug companies apply)

- **Dependent patents:** When a patent with significant technological progress of major economic impact depends on an earlier patent in order to be exploited, the new patent holder can request compulsory licensing of earlier patent (drug companies apply)

Patent holders are permitted to appeal compulsory license decisions within 3 months of notice

Outlook: Phase One trade deal hopes

Chen notes that recent events show that pharmaceutical patents in China lack teeth: "A reprimand from the securities regulator only affects the public statements of listed companies, it does not address the legality of manufacturing the API or formulation. For innovators holding Chinese patents, it doesn't help if the system would not stop unauthorized manufacturing and sales of a patented drug".

Recent Sino-US exchanges have produced commitment from China to introduce some of the fundamental changes demanded by innovative MNCs. The US-China Phase One trade deal signed in January 2020 included a string of pledges focused on IP including, Chen notes, three key pharmaceutical-specific provisions: to introduce a patent linkage system; establish patent term restoration in compensation for patent approval and product listing delays; and a promise to allow supplemental data to support patent filings.

National level promises to introduce patent linkage in China have been heard before. The former China Food and Drug Administration (CFDA) released draft plans to introduce a patent linkage system alongside China's Orange Book in May 2017, plans that the State Council appeared to approve weeks later. But while the China Orange Book was launched from early 2018, there has been none of the balanced Hatch-Waxman-style reforms initially promised and changes have favored generics players. There was no mention of 'patent linkage' in amendments to China's Patent Law issued in December 2018, or the amended Drug Administration Law (DAL) released in August last year.

Another key clause within the Phase One deal is China's commitment to preventing forced technology transfer. Chen notes that generics approvals prior to the expiration of the originator's patent could be viewed as a form of forced technology transfer: "IP protection means that NMPA approvals of generic drugs would come after the generic drug companies have obtained a license, the patent has expired, or has been invalidated. When the government regulator grants marketing approval before the expiry of the originator's patent, isn't that forced technology transfer?".

Chen cautions that the pledges made in the Phase One trade deal "are just promises at this stage". While the deadline for an action plan to implement the Phase One Deal was March 26, any substantive changes will take more time to become reality (or yet more unfulfilled promises). In the meantime, IP risks for drug innovators will remain high in China.