



An Analysis of Remdesivir Patenting

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Abstract

Pharmaceutical patents are categorized into primary patents and secondary patents. Primary patents refer to compound patents, while secondary patents mainly include crystalline form patents, process patent, formulation patent and method of use patent. In the recent outbreak of COVID-19, Wuhan Institute of Virology, has applied for a new method of use patent on Remdesivir for its efficacy and safety in the treatment of the pneumonia caused by 2019-nCoV. But Gilead Sciences, the inventor of Remdesivir, is the eligible holder of the compound patent of Remdesivir. In theory, the patent applied for by Wuhan Institute of Virology has utility and novelty rather than innovativeness, for which it may not be granted the method of use patent of Remdesivir. In this case, we suggest that the patent of Remdesivir be implemented through cross licensing and compulsory licensing between different patent holders.

Key words: Remdesivir; Pharmaceutical patents; Compulsory licensing

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The epidemic of the novel coronavirus 2019-nCoV detected in Wuhan, a central city of China, has spread around the country since the very beginning of 2020. At this critical moment, China's president Xi Jinping stressed the utmost importance of carrying out prevention and

control measures in a science-based, legal and orderly manner at the third meeting of the Commission for Overall Law-based Governance of the CPC Central Committee. Amid the combat against the epidemic, a debate has arisen over the application by Wuhan Institute of Virology, Chinese Academy of Sciences for a patent on the utility of Remdesivir, a possible cure for COVID-19. Certainly, how the debate is to be settled will influence the way prevention and control is conducted and how patients are treated in China. Thus, an in-depth analysis of Remdesivir patenting will shed light on the discussion of its method of use patent and furthermore help combat against the virus.

1. TYPES OF PHARMACEUTICAL PATENTS

The application filed by Wuhan Institute of Virology, as alleged, is for a patent on a new treatment method of Remdesivir. Patents on method of use belong to pharmaceutical patents. And compound patents, like the one Gilead Sciences obtained for its Remdesivir (CN103052631B) in China, represents the most important category in pharmaceutical patents for the fundamental role that compounds play in the invention of drugs. Furthermore, compound patents have various sub-categories including patents on basic compounds, prodrugs, pharmaceutically acceptable salts and active metabolites, etc. In fact, different types of patents can be applied for with different pharmaceuticals. For instance, a pharmaceutical company can apply for two drug patents respectively on drug A and drug B, and it is also the case for drug A and its active metabolites. If a newly invented drug has been granted the compound patent its inventor can become the monopoly seller of the drug.

Generally, a pharmaceutical patent is aimed to protect the products, formulation and uses that the patent holder invents. (Xiao, 2012) Compound patents are primary

patents, while the various patents derived from a patented compound are called secondary patents, which include crystalline form patents, process patents, formulation patents and method of use patents.

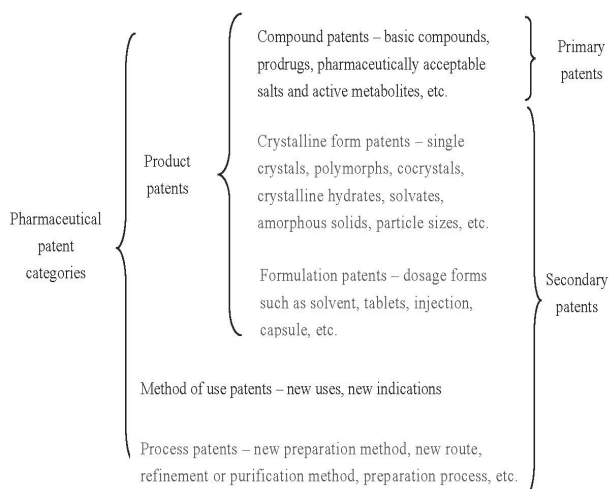


Figure 1
Types of pharmaceutical patents

A **crystalline form patent** is a patent on one of the different crystalline forms of a drug substance. For drugs with an identical chemical structure, different crystals can be obtained in different crystallization conditions. Improved crystalline forms will enhance the performance of a drug in quality and efficacy by optimizing its active ingredients, preparation stability, solubility and bioavailability. Crystalline forms, like those of Remdesivir patented in China, are common in pharmaceutical research and development and protection. In practice, crystalline forms of drugs that can be patented and protected include but are not limited to single crystals, polymorphs, cocrystals, crystalline hydrates, solvates, amorphous solids, crystalline forms of different particle sizes, etc. (Huang, Qian, et al, 2017) Yet so far, many problems in terms of the protection of pharmaceutical crystalline forms still remain unaddressed, among which the most prominent is the absence of a set of universal standards in the examination of the novelty of pharmaceutical crystalline forms. (Zhang, Ma, etc., 2016)

A **process patent** claims the process used to create or manufacture a drug. In many cases, there are more than one way to produce a drug. Gilead Sciences, for example, can apply for another process patent after it successfully achieves optimization in the manufacturing process of Remdesivir (CN107074902A) that it first invented, such as simplified manufacturing techniques, increased productivity and better performance in environmental protection.

A **formulation patent** claims the pharmaceutical dosage form of a drug, which means different dosage

forms of a drug might be granted different formulation patents. Gilead Sciences, again, can apply for another formulation patent with its newly invented sustained-release Remdesivir tablets though it has obtained one for its earlier Remdesivir tablets.

A **method of use patent** claims the “use of drug A to manufacture a pharmaceutical dosage form to treat disease B.” Examples are sildenafil, which was first a medication used to treat cardiovascular diseases before it was discovered to be effective for treating erectile dysfunction, and Remdesivir, which was originally invented for treating coronaviruses MERS and SARS and may possibly be used to treat COVID-19.

The four types of patents above are applied for at different points along the timeline of drug research and development. A proven inventor drug will always lead to the improvement of its manufacturing technique for lower costs, and the inventor will apply for a process patent on the technique to prevent potential infringement. An optimized dosage form or crystalline form of a drug based on clinical efficacy or in response to the clinical demands of other patients and the business strategy to expand market shares can also help the inventor to acquire a formulation patent and a crystalline form patent. If a new method of use is discovered after the drug goes into the market, the company can also apply for a method of use patent for it.

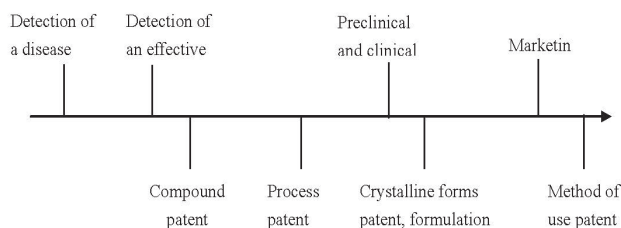


Figure 2
Patent cluster in the timeline of drug research and development

Method of use patents and medical diagnosis and treatment methods. According to China’s *Guidelines for Patent Examination*, a patent shall not be granted for a substance for use in medical diagnosis and treatment but for use in drug manufacturing. In other words, the invention of a substance for medicinal use is patented on the basis of a product claim or a manufacture method of use claim, such as “applications in pharmaceuticals” or “applications in the preparation of a drug for the treatment of a disease.” Accordingly, for method of use patent application in China, “substance A for use in the manufacture of the drug for disease B” must be clearly stated in claims instead of “substance A for use in the treatment of disease B.”

Method of use patent application is much more common in pharmaceutical chemistry than in other areas. For one thing, a change in a compositional element or a molecule structure may possibly result in a difference

in efficacy. In most cases, what effect a drug has when it is with a specific structure (or a family of structures) or a specific chemical formula (or a family of chemical formula) still remains unknown. Further efforts in in vitro cell experiments, animal experiments and clinical trials, therefore, are required to get closer to the exact efficacy a drug can deliver. So far, more than ten thousand kinds of diseases have been disclosed to the human world, with more being revealed continuously. The fact is, it would be impossible for humans to learn all the details of every disease, so the existence of an unknown use of a known drug is common. For another, it normally takes about twelve years and a huge amount of investment for a pharmaceutical company to go through the lengthy process from laboratory research to establishment in the market when it comes to the invention of a new drug. That's why pharmaceutical companies prefer to invest instead in a new use of a patented drug.

2. METHOD OF USE PATENT APPLICATION OF REMDESIVIR

Remdesivir, an antiviral drug invented by Gilead Sciences, an American pharmaceutical company, was originally used for Ebola virus infection before it was discovered to have antivirus activity against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

Amid the current epidemic, China's Wuhan Institute of Virology has discovered in its study that Remdesivir showed effects in suppressing the coronavirus, so on January 21st, 2020, the Institute filed its application for a patent on the new use of Remdesivir. This has since led to a heated debate among the public. Supporters believe that the Institute set a good example for the public by displaying a strong sense of intellectual property in its efforts to have its discovered use patented regardless of the result of patent examination. Meanwhile, the application is not an attempt for a bad-faith infringement of the patent acquired by Gilead, as the application was submitted on January 21st, 2020, ten days before the paper titled *Brief Report: First Case of 2019 Novel Coronavirus in the United States* was published. Thus, the new method of use invented by Wuhan Institute of Virology should be granted a method of use patent for its novelty and innovativeness as required in the Patent Law of the People's Republic of China. Furthermore, it is legitimate for the Institute to protect the interests of its country. What it is trying to do is to break up the monopoly of Remdesivir in the Chinese market, which it's started with a secondary patent of the drug. If successfully granted, the patent would be a bargaining chip in its cooperation with Gilead in research and development and in future cross-

licensing negotiations with pharmaceutical companies from other countries. (Liu, 2020)

On the contrary, dissenters argue that a simple trial with the published data from Gilead is sheer plagiarism. It lacks the "novelty and innovativeness" that an invention features and therefore should not be given a patent. They contend that the Institute is trying to safeguard its own interests rather than national interests, which may involve academic assessment and titles for researchers and patent application targets and material rewards for the Institute. If true, it comes completely against the purpose of patent legislation. Additionally, domestic pharmaceutical companies manufacturing and selling the Remdesivir for the treatment of the new coronavirus will have to obtain dual authorizations from both Gilead Sciences and Wuhan Institute of Virology if the patent is eventually granted. As to whether the new method of use will be made widely accessible without costs, that's unable to find out yet. (Xiong, 2020)

Both sides have their focus in this problem. Supporters believe, firstly, that the patent application by the Institute is a reasonable move, for the new use of Remdesivir it discovered in displaying suppressive activity against the virus demanded tremendous efforts in experiments with creativity. The inventor therefore has the right to apply for a patent for legal protection and it is not a bad-faith intent. But whether the patent will be granted depends on multiple factors.

Secondly, the patent that the Institute applied for is different from the ones Gilead had applied in China. According to our patent search, Gilead has legally acquired the patent on the compound of Remdesivir (CN103052631B) and the patent on the halogenated compound that is similarly structured with Remdesivir in China. Later in 2016 and 2018, the American company further applied respectively for the patent on the treatment of arenavirus and coronavirus infections and the patent on the polymorph and maleate form of the compound of Remdesivir, which are still under examination in China. As known, the compound patent acquired by Gilead is a primary patent while the method of use patent applied for by Wuhan Institute of Virology falls into the category of secondary patents. That means the two do not overlap at all. In practice, the compound patent of Remdesivir Gilead has obtained will remain effective and legitimate even if the application by Wuhan Institute of Virology later proves valid. Conversely, the examination of this method of use will be subject to the verdict that China's authority returns with regard to Gilead's application for the patent on the treatment of coronavirus infections.

Opponents, however, contend that the method of use patent applied for by the Institute should be not granted, for the innovativeness required for an invention is absent.

According to Article 22 of the Patent Law of China, “inventions and utility models for which patent rights are to be granted shall be ones which are novel, innovative and of practical use.”

As far as the authors are concerned, the new method of use discovered by Wuhan Institute of Virology does have practical use. As learned from the Patent Law of China, “practical use means that the said invention or utility model can be used for production or be utilized, and may produce positive results.” With the epidemic, researchers in the Institute detected the remarkable effect Remdesivir scored in dealing with pneumonia brought by 2019-nCoV from a large pool of candidates, which proves to have “practical use” as defined above.

In addition to practical use, this new method of use is also of novelty. Chronologically, the Institute filed its application on January 21st, 2020, ten days earlier than when the data about the antivirus activity that Remdesivir shows against the virus was published.

According to the public information from the National Genomics Data Center (NGDC), the overall sequence of the virus shares an 80.12% resemblance with that of SARS-CoV. That’s why its RDRP shows a significant difference from RDRP in the coronavirus family. The domain of Remdesivir works as competitor to inhibit RDRP. As a key enzyme for RNA virus replication, RDRP causes a decrease in viral reproduction by suppressing the activity of the virus. Therefore, the new use of Remdesivir (anti-2019-nCoV) cannot be directly revealed with the mechanism and pharmacological effects of the previously known uses against other members of the coronavirus family. Moreover, the new use differentiates more than just in the dosage, time, and frequency in the drug delivery. All these combined to suggest that the new use is substantially different from the previously known ones and it is an addition to the known uses of Remdesivir.

As China’s *Guidelines for Patent Examination* suggests, the disclosure of general (high-level) concepts is not prejudicial to inventions defined by specific (lower-level) concepts. For instance, the difference between a claimed invention and a reference document is that “halogen” or another specific halogen “fluorine” in the reference document is replaced by “chlorine” in the invention claim, so the disclosure of “halogen” or “fluorine” in the reference document is considered as non-prejudicial to the invention defined by “chlorine”. Accordingly, despite the fact that Gilead Sciences applied for a patent for coronavirus infections treatment, the new use patent of anti-2019-nCoV Wuhan Institute of Virology applied for is a prejudicial disclosure to that of anti-coronaviruses, as 2019-nCoV belongs to the coronavirus family, a higher-level concept.

Finally, the patent for the use of Remdesivir from Wuhan Institute of Virology is not considered

innovative. According to the *Guidelines for Patent Examination*, a new use of a known product is considered to be innovative when it is derived or can be predicted obviously from the structure, composition, molecular weight, known physicochemical properties and the current uses of the product and is used to produce unpredictable technical effects with the newly discovered properties of the product. Thus, the innovativeness of an invention is the key to the “obviousness” and “unpredictable technical effects” that a new use features. It is also pointed out in the *Guidelines for Patent Examination* that to determine whether the claimed invention is “obvious” to the prior art, the following three steps need to be performed: determine the closest prior art; determine the distinctive features of the invention and the technical problems that the invention solves; and determine whether the claimed invention is obvious to those skilled in the art. As for “unpredictable technical effects”, it requires more than just differences or changes to previous technical effects. The most critical and indispensable requirement is “unpredictability”, which needs to be evidenced by experimental data. (Zhang, 2012)

Gilead Sciences applied for a patent for the treatment of arenavirus and coronavirus infections (CN108348526A) in China in 2016 and made it public on July 31, 2018. Relevant vitro cell experiments and animal model experiments both proved that Remdesivir has antiviral effects on SARS-CoV and MERS-CoV (Table 3 and Table 4). In a paper from Wuhan Institute of Virology that was published on *Cell Research*, it says “studies show that in VeroE6 cells, EC50 of Remdesivir (GS-5734) is 0.77µM and its SI is greater than 129, while EC50 of Chloroquine is 1.13 uM and its SI is greater than 88. These numbers indicate that the two drugs above can effectively inhibit COVID-19 infections at the cellular level, but their effects on the human body still need to be clinically verified” (Figure 5).

Table 3
In Vitro Experimental Data of Remdesivir (compound 32) Directed against MERS Disclosed in Gilead Sciences’ Patent Application¹

	EC50 (µM)
Determination	
Virus	MERS-CoV
Cell Line	Vero
Compound 9	0.46
Compound 32	0.58

¹The treatment of arenavirus and coronavirus infections. <http://epub.sipo.gov.cn/patentoutline.action>. February 20th, 2020.

Table 4
Antiviral activity and cytotoxicity of compound 1 and compound 32 against MERS-CoV and SARS-CoV²

0	EC50 (μM) ¹		CC50 (μM)
	MERS	SARS	
Compound 1	0.46 (HAE) --(Calu-3)	0.22 (HAE) --(Calu-3)	>100 (HAE) >100 (Calu-3)
Compound 32	0.074 (HAE) 0.03 (Calu-3)	0.069 (HAE) 0.01 (Calu-3)	>10 (HAE) >10 (Calu-3)

All the data are the average of more than 3 independent experiments. HAE=Human Airway Epithelial Cells. Calu-3=A human lung cancer line cell Calu-3 (Calu3-2B4). HAE research was accomplished by three donors.

In vitro experimental data of remdesivir (compound 32) directed against MERS and SRAR disclosed in gilead sciences' patent application.

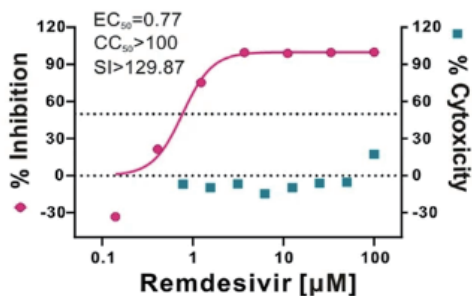


Figure 1
In vitro experimental data of remdesivir in vero E6 cells in the paper by Wuhan institute of virology (Wang, Cao, Zhang, et al., 2020)

COVID-19 is a member of the coronavirus family, though it shares a mere 80.12% sequence identity with SARS-CoV. Based on the structure, composition, molecular weight, and known physicochemical properties of Remdesivir, together with its experimental designs and valid data in SARS-CoV and MERS-CoV (both have been published), the idea that Remdesivir has a therapeutic effect for treating COVID-19 can be accordingly confirmed. This leads technical personnel in the field of biomedicine to perform relevant experiments on the drug. Table 3 and Figure 1 show that the control group in the experimental design of Wuhan Institute of Virology has previously emerged in the in vitro cell experiments of Remdesivir directed against coronaviruses, which suggests a remarkable similarity between these two experimental designs. As far as the authors are concerned, this case is in line with what the *Guidelines for Patent Examination* stipulates, “what needs to be determined is whether there is some technical revelation in the prior art as a whole. That

²The treatment of arenavirus and coronavirus infections. <http://epub.sipo.gov.cn/patentoutline.action>. February 20th, 2020.

is to say, to determine whether the prior art reveals such distinguishing features mentioned above that can be applied to the closest prior art to solve its existing technical problems, which means the technical problems can be solved by the invention. This kind of revelation will motivate those skilled in the art to improve the closest prior art and obtain the claimed invention when they are facing the technical problem. If such technical revelation exists in the prior art, the invention to be claimed is considered as obvious and does not have outstanding substantive features.” Therefore, the invention claimed by Wuhan Institute of Virology is obvious.

As shown in the results of the in vitro cell experiments, Remdesivir has a comparable antiviral effect on COVID-19 and MERS. (Table 6) (As the cells used in the in vitro cell experiments of Remdesivir against SARS-CoV are different from those for the novel coronavirus, comparison will not be made here.) However, the antiviral effects of Remdesivir on COVID-19 and MERS are consistent, and there was no discovery of new physical or chemical properties of Remdesivir. Except for the viruses, other experimental data, including mechanism and physical properties of Remdesivir, are mostly the same as those from Gilead Sciences. Thus, the process and results of the experiments presented in the experimental data from Wuhan Institute of Virology are predictable.

Table 6
Comparison of antiviral activity of remdesivir between novel coronavirus and MERS

Remdesivir	EC ₅₀ (μM)
2019-nCoV	0.77
MERS	0.58

To summarize, the invention filed by Wuhan Institute of Virology is apparently “obvious” and does not produce “unpredictable technical effects” and thus is deemed to be non-innovative according to the *Guidelines for Patent Examination*. That means it may not be patented as an invention against the novel coronavirus.

3. THE IMPLEMENTATION OF REMDESIVIR PATENTS

Remdesivir patents, either compound patents or method of use patents, carry their values in implementation. In the combat against the 2019-nCoV, compulsory licensing and cross licensing may both be used in the implementation of Remdesivir patents.

3.1 Compulsory Licensing

In the Patent Law of China, Article 49 says “where a national emergency or any extraordinary state of affairs occurs, or public interests so require, the patent administration department under the State Council may grant a compulsory license for exploitation of an invention

patent or utility model patent.” Accordingly, the following conditions must be satisfied if compulsory licenses are to be used.

Firstly, the patents, either compound patents or method of use patents, must be granted by China’s authority. Otherwise, inventions will not be subject to compulsory licensing if not patented like the one on the treatment of arenavirus and coronavirus infections or the other on the polymorph and maleate form of the compound of Remdesivir.

Secondly, compulsory licenses can only be granted and used in a national emergency and extraordinary situation to protect the public’s interests. If, under extreme circumstances, the patentee opposes the compulsory license in defiance of public health, national authorities have the right to restrict the legal rights of the patent holder (Hu & Xu, 2005) by compulsory licensing.

Lastly, compulsory licenses shall be granted by China’s National Intellectual Property Administration, the patent administration department under the State Council, rather than that of the municipal government of Wuhan or the provincial government of Hubei.

With these three conditions satisfied, it will still depend largely on actual situations as to whether the National Intellectual Property Administration will grant a compulsory patent or not. The inventor of Remdesivir, Gilead Sciences, has made a clear announcement that all Remdesivir provided for clinical trials in China would be free of charge. Thus, no compulsory licenses are needed in this case.

3.2 Cross licensing

In the case where a new use of an established drug is patented while the product patent of the drug belongs to another party, a cross-licensing agreement is required in the implementation of this patent. “Cross licensing is a licensing method where patentees exchange licenses so that they can access the invention of the other party.” (Liu, 2014) It is believed that if the patent application by Wuhan Institute of Virology is approved, the Institute can reach a cross-licensing agreement with Gilead on the compound patent (CN103052631B) and the method of use patents of Remdesivir. From the authors’ point of view, this cross-licensing is theoretically possible. For one thing, whether the patent applied for by the Institute will eventually be granted still remains pending. For another, Gilead may not have to obtain the license from the Institute even if it is granted. As the 2019-nCoV is a member of coronaviruses, it is possible that superindication medication, also called off-label drug use, exists in clinical treatment. (Yao, 2012) In this case, Gilead does not need a cross license from the Institute. Normally, a drug information leaflet is composed based on the content in the patent

specification of the drug. In its patent specification, Remdesivir’s efficacy description should be “used to treat infections caused by coronaviruses” instead of “used to treat 2019-nCoV infections.” With Remdesivir effective in treating the novel coronavirus, physicians can exercise their right to prescribe Remdesivir in confirmed cases without the authorization from Wuhan Institute of Virology. Meanwhile, superindication medication does not make a medical infringement unless there is medical malpractice in the process. Therefore, it does not matter whether Gilead is given a license from the Institute even if the patent application for the new use against 2019-nCoV is approved.

Still, more questions are raised: can Gilead’s patents on Remdesivir be implemented in China for the treatment of COVID-19? Can China’s National Intellectual Property Administration grant a compulsory license? If yes, is it an infringement of Gilead’s patent? Our answer is intellectual property right is a regional or national concept, which means “intellectual property rights acquired in accordance with the laws of a country are valid only in that country and carry no legal effect in other countries.” (Wu, 2003) Accordingly, the patent rights of Remdesivir granted by US authorities will be only protected by US Patent Law and carry no legal effect in China as it is not patented in the country. So, inventors should have their inventions patented in accordance with the international intellectual property treaties, bilateral agreements, multilateral agreements or the principle of reciprocity and the patent laws of some certain countries or regions if they desire to obtain patent law protection for their inventions there. Furthermore, if a pharmaceutical company produces and sells Remdesivir during the epidemic in China, the behavior of the pharmaceutical company is not an infringement of patent rights even without the permission of Gilead, as the American company does not enjoy patent rights in China. It is possible that the move of the pharmaceutical company falls into the area of unfair competition and will be regulated according to China’s Anti-Unfair Competition Law. Last but not least, a drug patent is the prerequisite for drug compulsory licensing, so it is impossible to grant a compulsory license for a patent on a drug invention that has not been applied for (obtained) in China.

REFERENCES

- Hu, X. H., & Xu, J. (2005). On the legitimacy and the principles of restrictions on the basic rights of citizens. *Law Review*, (6).
- Huang, L., Qian, L., etc. (2017). Patent Protection and Patent Strategy in Pharmaceutical Industry. *Chinese Journal of New Drugs*, (2).
- Liu, C. Q. (2020). *Chinese research institute’s patent application is not a bad-faith infringement*. Retrieved 26th February 2020 from <https://www.yicai.com/news/100491185.html>.

- Liu, C. T. (2014). *Intellectual property law*. China Renmin University Press.
- Wang, M. L., Cao, R. Y., Zhang, L. K., et al. (2020). *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*. Retrieved 20th February 2020 from <https://www.nature.com/articles/s41422-020-0282-0>.
- Wu, H. D. (2003). *Intellectual property law*. Law Press-China.
- Xiao, X. X. (2012). New chemical entity drug patent layout strategy – A case study of AstraZeneca’s patents on Gefitinib in China. *China Invention & Patent*, (1).
- Xiong, W. C. (2020). *An analysis of the remdesivir method of use patent filed by Wuhan institute of virology*. Retrieved 26th February 2020 from <https://mp.weixin.qq.com/s/m6r67Z8lJ6rFsixE9vH0TA>.
- Yao, L. (2012). *Is “Off-Label Drug Use” A medical infringement?*. *Medicine Economics Report*, (5).
- Zhang, H., Ma, Q. J., etc. (2016). Discussion on the Novelty of Patents on the Crystalline Form of Drugs. *Chinese Journal of New Drug*, (5).
- Zhang, P. (2012). *Principles and practices of patent authorization and confirmation system*. Intellectual Property Publishing House.