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REVIEWS

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## SARS-CoV-2 and Patent Activity

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**Abstract**—The article provides information on the patent activity of inventors in relation to applications for inventions related to coronaviruses, in particular, to SARS-CoV-2. The presence of a steady interest in this topic for the period 1996–2020 is illustrated. It is indicated what objects of patent law can be inventions related to vaccines.

**Keywords:** patent law, coronavirus, SARS-CoV-2, invention

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As is known, in March 2020, the WHO declared a pandemic for SARS-CoV-2. But even before this event, since the very beginning of 2020, the whole world began to follow the development of events in China. Thus, the beginning of 2020 was marked by the fact that not only specialists learned about the existence of coronaviruses, but also ordinary people. Virologists have known about coronaviruses since 1937, when the first coronavirus was discovered. It was the avian infectious bronchitis virus (IBV). On the other hand, human coronaviruses have been known since the 1960s. However, these viruses did not receive much attention [1].

The first human coronavirus was isolated by D. Tyrrell and M. Bynoe in 1965 from a patient with acute rhinitis. Until 2002, coronaviruses were considered to be the causative agent of mild rhinitis in humans [2].

The family Coronaviridae now comprises 39 species of coronaviruses, each of which includes tens and hundreds of strains. In addition, there are ten other species that are potential coronaviruses. Specialists are still only verifying whether they can be considered true coronaviruses [1]. Currently, six species of coronaviruses are pathogenic for humans [2].

Coronavirus is an RNA virus. The family Coronaviridae includes two subfamilies: Coronavirinae and Torovirinae. Viruses from the subfamily Coronavirinae, which includes the genera Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, cause various forms of acute respiratory infection. Viruses from the subfamily Torovirinae, which includes the genera Bafinivirus and Torovirus, are the causative agents of gastrointestinal diseases [2].

The public first turned its attention to coronaviruses in 2002, when there was an epidemic of severe acute respiratory syndrome (SARS) with a case fatality rate of  $9.60 \pm 0.32\%$  in 30 countries [3]. The culprit of the epidemic was a new strain of coronavirus called SARS-CoV. In 2015, the coronavirus again started an epidemic caused by a variant of the coronavirus called MERS-CoV with a case fatality rate of 35%. And now, in 2020, a rapidly spreading pandemic caused by a mutated strain of SARS-CoV, called SARS-CoV-2, with a 2020 case fatality rate of about 2% [2]. Interestingly, all three strains that caused mass deaths belong to the genus Betacoronavirus.

Despite the fact that the public first learned about coronaviruses in 2002 and did not pay close attention to it until 2020, specialists knew about the virus. The reason is that the natural hosts of coronavirus are a wide range of vertebrates, mostly mammals and birds. And also, among acute respiratory infections, coronaviruses occupy 4–20% [2], and according to some reports, up to 30% [1]. Therefore, the development of drugs and methods to both prevent and treat coronavirus infections, as well as the development of test systems to diagnose coronavirus infections, has long been underway.

As is known, one of the stages in the journey of a drug from its creation to the consumer is the acquisition of the exclusive right to the drug. In other words, a drug must be patented before it can be put on the market.

It is clear that the development of the pharmaceutical industry is also reflected in the way intellectual property created during drug development and clinical trials is protected. The pharmaceutical industry pays special attention to patent protection. This is because

drugs are in demand. They can be easily copied and reproduced, and are attractive to both falsification and counterfeiting. To minimize the risk of losing the opportunity to use their development, reputational losses, acquiring the tools to dispose of the rights to their development, and the technologies created need to be patented.

Patent law provides a wide range of opportunities to patent various aspects of the created technology. For example, it is possible to obtain an exclusive right to a drug (active ingredient), a manufacturing process, or a composition or a combination [4, 5]. In addition, the patent legislation of the Russian Federation also allows obtaining a patent for a method of medical treatment, which is not possible in all countries. Test systems for diagnosing diseases and the specifics of their use can also be patented.

An important part of the fight against viral infection is taking measures to prevent its spread. Vaccination is the best means of preventing many viral diseases. Vaccines, their manufacturing processes, and their methods of use are also subject to patents.

We analyzed the period from 1996 to the 3rd quarter of 2020 regarding patent activity for coronaviruses.

From 1996 to the present, with the exception of 2002, patent applications for decisions related to coronaviruses have been submitted to Rospatent at a regular rate. The data we analyzed shows that the interest of applicants in this area was at a constant level for a long time, being in the range of 1–5% of all applications submitted regarding viruses. In 2020 alone, there was an explosive growth of interest in this field, reaching 58% of all patent applications related to viruses in the first 8 months.

How significant is the number of 1–5% of patent applications from all applications related to viruses? The answer to this question can be obtained by looking at filings on a topic that applicants are consistently interested in, such as influenza. Influenza-related applications account for 7–20% of the total number of virus-related applications. Thus, we can conclude that interest in the topic of coronavirus in Russia has always been and has even reached rates comparable to interest in such in-demand areas as influenza treatment, prevention, and diagnosis.

Interestingly, in 2003, when the SARS-CoV-1 epidemic broke out, the popularity of influenza and the popularity of coronavirus topic began to trend toward each other. The number of applications filed related to the treatment, prevention, and diagnosis of influenza was almost the lowest in the period under review, at 7%, and one of the highest for those related to coronavirus, except for 2020, at over 4%. This high interest in coronaviruses lasted until 2014. Surprisingly, the MERS-CoV epidemic with a 35% case fatality rate did not boost patent activity for the coronavirus. So, patent activity, after dropping to 3% in 2015, with a slight uptick in 2016, continued to decline through 2020.

According to the WHO, immunization is a proven tool for fighting infectious diseases. Immunization prevents 2 to 3 million deaths each year. It is one of the most cost-effective investments in health care with proven strategies that make immunizations accessible to even the most hard-to-reach and vulnerable populations [6].

Patent activity is one of the indicators of development of various directions in a particular field of technology. Patent information in general and a patent for an invention in particular are used at all stages of the life cycle of technical objects. The patent establishes the priority, and the patent information is used to develop technical innovations, to determine the prospects of commercialization of the created objects of industrial property and their competitiveness, to solve the issues of promotion of new objects of technology on the market, and to ensure their patent clearance [10]. Thus, of particular interest in the structure of patent activity is the question of how many applications are filed related to immunogenic compositions aimed at creating immunity against coronaviruses.

Analysis of data from 1996–2020 showed that from 1996 to 2001, nearly 100% of coronavirus-related patent applications were for potential vaccines. Surprisingly, this dropped to 43% in 2003 and has continued its decline to the present, peaking at 50% only in 2018. Of all applications for inventions filed for technology of fighting against coronavirus infection, such as technology relating to both the immunogenic compositions themselves and the manufacturing process of said compositions and their components, technology relating to methods of treatment, technology relating to both the test systems themselves, and their methods of use, the year 2020 accounts for 15% of applications for potential vaccines.

As is known, existing vaccines can be divided into two types: attenuated (live) and inactivated, including subunit vaccines. Each type of vaccine has its own disadvantages and advantages. Therefore, attenuated virus strains and whole-virion attenuated vaccines are still used, along with the latest vaccine technologies. For example, the Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products, Russian Academy of Sciences followed this path to create a vaccine against SARS-CoV-2 [15]. Examples of patents on vaccine strains of coronaviruses are RU 2263144, RU 2100433, or RU 2399668. Not only a vaccine strain can be patented, but also a vaccine containing such a strain. In this case, examples relating to coronaviruses may be: RU 2211705, RU 2137499, or RU 2301079. It should be noted that if the immunization process of the claimed vaccine has any peculiarities, or if some immunization scheme is most preferred, then of course a method of immunization or method of treatment may also be patented, either together with the vaccine or in a separate application, based on the applicant's purposes. This cir-

**Table 1.** Example of SARS-CoV-2 related application processing time at Rospatent and at the Chinese Patent Office

	Rospatent	Chinese Patent Office (SIPO)
Application number	2020114424	202010193587.8
Priority date	April 23, 2020	March 18, 2020
Decision date	April 27, 2020	August 11, 2020
Publication date	May 12, 2020	June 2, 2020
Title of invention	Immunobiological agent and a method for use thereof for inducing specific immunity against the SARS-CoV-2 severe acute respiratory syndrome virus (versions)	A recombinant new coronavirus vaccine using human replication-deficient adenovirus as a vector
Patent owner	The Gamaleya National Center of Epidemiology and Microbiology	The Academy of Military Medical Sciences of the Chinese People's Liberation Army and CanSinoBiologics Inc

cumstance applies not only to vaccines containing attenuated strains, but also to any vaccine, and the features of the immunization or treatment process can be expressed both through the object "Method" and through the object "Application." Such patenting tends to be carried out by foreign applicants, for example, RU 2400248 and RU 2595873. At the same time, of course, the method of obtaining the strain, if it is a mutant strain, or vaccines are also subject to patent rights, as reflected in RU 2689671 and RU 2440123.

In the case of subunit vaccines against viruses, one approach to their production is the use of different expression systems for the rapid production of individual viral proteins in preparative quantities [7]. Here, the subject matter of the patent rights for the invention may be the vaccine itself and its components, or the method of producing the components or the method of producing the vaccine itself, furthermore, the use as a method/application of the components and/or the vaccine. These objects can be presented as separate applications or combined into one.

A particularly successful example of such protection is RU 2723008, which reflects a comprehensive approach to patenting an integral technology.

A disadvantage of both traditional subunit vaccines and recombinant subunit vaccines is low immunogenicity [8]. Immunogenicity of vaccines can be increased, for example, by using viral vectors, which are recombinant viruses that have a target gene embedded in their genome with a set of regulatory elements. Among the existing antigen delivery systems, viral vectors occupy a special place, since they have the following properties: they have a natural mechanism of interaction with the cell and penetration into it; they carry foreign genetic material into the cell nucleus; they can ensure long-term antigen expression; and the viral shell protects the genetic material encoding the antigen. Vaccines based on viral vectors effectively activate cytotoxic T lymphocytes, which is especially important for vaccination against intracel-

lular pathogens. Viral vectors have the ability to activate innate immunity [8]. In this case the object of patent rights may be a product: a gene; a protein encoded by this gene; a vector containing such gene; a vaccine containing the vector, as well as the object relating to methods and/or applications: a method and/or application for treatment, a method of producing any of the said products, a method of using any of the said products, and application of any of the said products.

Each of the above-mentioned objects may be claimed either alone or in various combinations. Examples are patents: RU 2720614, RU 2731342, and RU 2731356.

The analysis of information to determine which vaccines are currently developed and for which applications have been filed shows the following.

According to WHO data from July 31, 2020, there were 29 candidate vaccines in various stages of clinical trials and 138 candidate vaccines in preclinical trials.

Of the 29 candidate vaccines, 6 are viral vector-based vaccines. Of these, 5 were designed on the basis of an adenovirus: vaccines from Institut Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme are based on the measles virus, and the Gam-COVID-Vac vaccine developed at the Gamaleya National Center of Epidemiology and Microbiology on the basis of human adenovirus. The latter received patents of the Russian Federation for invention № 2720614, № 2723008, № 2731356, and № 2731342.

Other adenovirus-based vaccines have been developed:

- 1) University of Oxford (UK)/Astra Zeneca (UK-Switzerland) based on chimpanzee adenovirus [13].
- 2) CanSinoBiological Inc./Beijing Institute of Biotechnology (China) based on the human adenovirus. Patent application CN111218459 was published on 02/06/20 [14].
- 3) Janssen Pharmaceutical Companies (Belgium, USA) based on human adenovirus [11].

4) ReiThera (Italy)/LEUKOCARE (Germany)/Univercells (Belgium) based on gorilla adenovirus [12].

It must be said that the choice of adenovirus for vaccine development was not accidental. Adenoviruses possess important properties for vaccine vectors as the ability to provide a high level of expression of the target transgene in the target cell and to transduce both mitosis and postmitotic cells. At the same time, adenovirus DNA remains in extrachromosomal form. Adenoviruses are capable of accumulating in high titers in cell cultures [9]. The process of obtaining a new recombinant adenovirus takes several weeks, allowing a response to the changing epidemiological situation as quickly as possible.

The vector vaccine developed by the Gamaleya Center, which has been granted patent protection in the Russian Federation, is not the only development of domestic scientists in this field. State Research Center of Virology and Biotechnology Vector, one of the leaders of patenting in the virus cluster, which during the analyzed period filed about 200 applications, out of six variants of the future vaccine: three vector vaccines, subunit vaccine, mRNA vaccine, and peptide vaccine, in the end chose the peptide vaccine. Chumakov Center also proposed a decision by offering a whole-virion vaccine [15].

A legitimate question arises: why were vaccines created so quickly in Russia?

This can be answered by analyzing patent activity on the cluster of virus-related applications in the Russian Federation.

The creation of modern biotechnological products takes place at the intersection of several fields. Thus, if we talk about modern vaccines, it is not enough to have a detailed knowledge of the virus from which the vaccine is being created, and to be able to work with this virus. It is necessary to select a delivery vector or expression system that will combine a number of desired functions, have minimal disadvantages, and be compatible with the components of the virus of interest. For example, the Gamaleya Center and the State Research Center of Virology and Biotechnology Vector point out that the development of a vaccine against SARS-CoV-2 within such a short period of time became possible thanks to their work on the Ebola virus [15], although the State Research Center Vector also has results on coronavirus patented in Russia, including No. 2473702 dated 01/27/13 and No. 2504585 dated 01/20/14. Thus, if a company or research center has a large number of developments relating to viruses in its research portfolio, it is more prepared to face the most unexpected new challenges in this area of science.

The race to create vaccines now includes not only the major players in the pharmaceutical market, but also teams of scientists from different countries, which reflect the interests of states. Given these circumstances, the patent offices of the world are also included in the forced competition. On the one hand,

they provide information about the innovations being created, and on the other hand, they have initiated a fast-track procedure for applications related to the fight against coronavirus infection.

The value of the information disclosed in patent documents is due to the fact that it is the patent documents that first of all describe in detail the created innovation, for example, the active ingredient of a new drug and its unexpected properties, the design of the created device, and the principle of its operation; the sequence of procedures aimed at rapid treatment of a disease; a set of diagnostic factors that allow to identify with high accuracy the disease in its early stages, etc.

Patent documents are clearly structured texts containing certain sections. All patent documents are classified according to an international classification. Because of the classification of each patent and the existence of a uniform structure of a patent text for most patent offices around the world [10], a search in the patent documents allows you to quickly and accurately find the required information.

Because patent offices around the world exchange information on patent documents, information about a registered invention in one country quickly becomes available to scientists from around the world.

An example is obtaining a patent for a vaccine at the Russian and Chinese patent offices. These applications for an invention were filed almost simultaneously and both were considered under the high-priority fast-track procedure.

Since the Russian invention was mentioned above, it makes sense to look at the proportion of Russian applicants in patent applications related to coronavirus. It will help to understand the significance of this proportion and compare it to the proportion of domestic applicants in all virus-related applications.

From the data analyzed, we can see that in the period before 2004, domestic applications dominated in the coronavirus-related cluster, showing a drop in interest only in 2002. In 2005–2007, there was a decline in activity in patenting domestic inventions related to coronavirus. This is followed by a three-year spike in activity and then a definite decline until 2018. In general, the interest of domestic applicants in patenting in the virus-related cluster is high. It was low only in 2004–2006 and 2014. It must be said that the growth in applications by domestic applicants in both the virus-related cluster in general and the coronavirus-related cluster resumed in 2019 and continued in 2020.

Meanwhile, interest in patenting decisions related to coronavirus in Russia did not change much in 2003 and 2015, when there were epidemics of coronavirus. However, in 2020, there has been an explosive growth in interest from domestic applicants in the possibility of patenting decisions related to the new SARS-CoV-2 coronavirus.

According to the data presented, domestic applicants pay attention to patenting decisions related both

to viruses in general and coronaviruses in particular. At the same time, the tendency to patent such technical decision has a steady interest. Interest in patenting coronavirus technical decisions changed little in 2003 and 2015, during the period of the coronavirus epidemic. However, in 2020, there has been an explosive growth in interest from domestic applicants in the possibility of patenting decisions related to the new SARS-CoV-2 coronavirus. Since interest in patenting vaccines against coronavirus or immunogenic compositions that are potentially vaccines has also been consistent over the past 24 years, this circumstance may have contributed to the fact that decisions that could potentially lead to a vaccine have now been proposed so quickly.

#### COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

#### ADDITIONAL INFORMATION

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