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Monoclonal antibodies for Covid-19: a patent analysis

Gli anticorpi monoclonali per il Covid-19: un'analisi brevettuale

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INDEX

SOMMARIO

Lo scopo di questo di questo elaborato è quello di analizzare da un punto di vista brevettuale e di regolamentazione la situazione globale degli anticorpi monoclonali come terapia al Covid19.

La necessità di tale studio nasce dal problema pandemico creato dal Sars-CoV-2 nel recente periodo e dal riconoscimento dell'importanza di tali terapie nel settore sanitario.

Inoltre, l'enorme valore informativo dei brevetti ci permette di poter identificare il livello di conoscenza in diversi settori. Difatti, i brevetti vengono considerati indicatori promettenti di conoscenza tecnologica utilizzati nella ricerca innovativa, mentre vengono spesso sottovalutati come risorse nelle scienze biologiche.

Dopo una presentazione degli anticorpi monoclonali, della struttura del Sars-CoV-2 e del processo brevettuale, l'elaborato si concluderà con un'analisi dedicata al panorama dei brevetti nelle terapie a base di anticorpi monoclonali per questo specifico virus.

Per raggiungere tale obiettivo, sono stati utilizzati i databases brevettuali "Espacenet" dell'European Patent Office (EPO) e "Patentscope" della World Intellectual Property Organization (WIPO). A questi dati sono stati affiancati indicatori bibliometrici per poter analizzare e interpretare i risultati. Questi hanno evidenziato la presenza eccezionale della Cina e delle loro istituzioni accademiche e governative in questo specifico settore.

ABSTRACT

The aim of this work is to provide a patent analysis and an overview of the regulation practices regarding the monoclonal antibodies (mAbs) therapy for Covid19.

The need behind this study arises from the health emergency carried out by the pandemic derived from the spread of the Sars-CoV-2 virus in the latest period. This aspect, in conjunction with the relevance of those therapies in the health care sector for different diseases, set the basis of the present work.

Moreover patents are an incredible source of information for researchers and professionals to define the level of knowledge and they are indeed considered valuable technological knowledge indicators. However, it should be stated that their importance is often underrated as resources in biological sciences.

For this reason, the monoclonal antibodies, and the structure of the Sars-CoV-2 together with the patenting process are going to be presented in this work. Then, the dissertation will exhibit an analysis of the patent landscape of monoclonal antibodies therapies for Covid-19. In order to reach this goal a dataset has been created. The original data are from “Espacenet” and “Patentscope” , respectively the patent dataset of the European Patent Office (EPO) and that of the World Intellectual Property Organization (WIPO). In addition, to analyze and interpret the results, bibliometric indicators have been employed. The results have shown the leading role of academic and government Chinese institutions in this sector.

INTRODUCTION

During March 2020 a new coronavirus reshaped habits and economics of the countries all over the world. This virus is now known as Severe Acute Respiratory Syndrome Coronavirus 2 (henceforth Sars-CoV-2) and it originated in China. The virus has circulated all over the world and the characteristics of this new disease have put the sanitary systems of all countries under pression leading to a pandemic situation declared by the World Health Organization (WHO) on the 12th of March 2020. As a consequence, to contrast the virus, some therapies have been adapted and developed. One of them is based on monoclonal antibodies (henceforth mAbs). The aim of this project is not to provide a medical point of view of this therapy. Indeed, the final goal is to be able to utilize the patent and regulation analyses to evaluate the state of knowledge in this field and sector. Therefore, this dissertation will be answering to research questions regarding the inventors behind the creation of these monoclonal antibodies for therapeutical treatment of Covid-19. Moreover, it will take into consideration the countries that took part in these patent applications and the reasons that have probably caused the current trend, leaded by one of them. It will focus on the major contributors, if they represent the public or the private sector and if there are some pharmaceutical companies that exhibit a major interest in the mAbs patenting process. Finally, these patents will be evaluated using bibliometric indicators and the information contained within them, for instance through the use of backward and forward citations to provide a quality review.

However, to reach this goal a scientific introduction on the monoclonal antibodies (mAbs) is needed. Indeed, the first chapter reviews the history of the monoclonal antibodies, their use in the health sector during these years and their structural characteristics. MAbs are laboratory-created proteins first introduced around 1975 (Kohler et al., 1975). As for Buss et al. (2012), those antibodies can have several applications in the health care sector due to their peculiarities and low by-product. For all these reasons, the employment of mAbs has been extended to the treatment of the Sars-CoV-2 virus. In this chapter a rapid overview of the virus is also given from a biological perspective focusing on the clinical characteristics responsible of its transmission among individuals. In particular, the Sars-CoV-2 belongs to the Coronaviridae family, which can be subdivided into genera. The current one is part of the Beta-coronaviruses, which are the ones caused by zoonotic infections. The disease that derives from this virus is called Covid-19 (Beig Parikhani et al., 2021). Finally, the first chapter ends with the description of how the mAbs can be used to treat Covid-19, from a biological point of view. Indeed, thanks to their adaptability they represent a weapon against the Covid-19. Monoclonal antibodies can do that since they can lower the viral load of the virus that is trying to attack the human body, linking to the Spike protein neutralizing the infection (Taylor et al., 2021).

The second chapter depicts the process of introducing a new drug into the market, starting from the recognition of the importance of the intellectual property and the patents. A patent is not only a protection instrument that grants the rights to exclude

others, but also an inventive indicator that encourages in an indirect way the research. After analyzing the patent advantages and disadvantages, the chapter describes the differences among the patenting process between Europe, which has to follow the standards described in the European Patent Convention (EPO, 2020), and the USA, based on the principle of "first inventor to file" (ICE, 2016).

Then, the importance and characteristics of patents in the pharmaceutical sector are highlighted. Pharmaceutical companies have several types of patents that can be used to protect their products. Also, it follows an introduction to the two main authorities: European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Those authorities follow different provisions regarding the exclusivity rights in Europe and USA.

Furthermore, the analysis and presentation of the eight patentability criteria regarding the mAbs by Germinario et al. (2018) are depicted. Authors describe this patenting process as a challenge since the patentability depends on the antibodies ability to connect with an epitope of a specific antigen.

The chapter continues by describing the process of introduction of the drugs into the market, focusing on the different principles established by the respective authorities in Europe and United States. It concludes with a digression on the Emergency Use Authorization (EUA) and the extraordinary measures adopted in the countries for the specific case of monoclonal antibodies for Covid-19.

The third chapter presents the empirical analysis. The study starts with a review of the bibliometric approach and the importance of some information that can be collected only from patents and analyzed according to indicators. That information, according to the OECD Patent Manual, can be classified into: technical description, development and ownership, or information related to the history of the application. Then, according to Donthu et al. (2021), the bibliometric indicators could be classified into “performance analysis” and “science mapping”. This representation is considered the basis and the starting point of our analysis for the indicators. Then, the chapter goes on with the description of the methodology, showing the key words chosen during the research and the screening principles adopted. The chapter ends with the representation of the results through graphical tools and tables.

CHAPTER 1: MONOCLONAL ANTIBODIES AND SARS-COV-2

1.1 MONOCLONAL ANTIBODIES

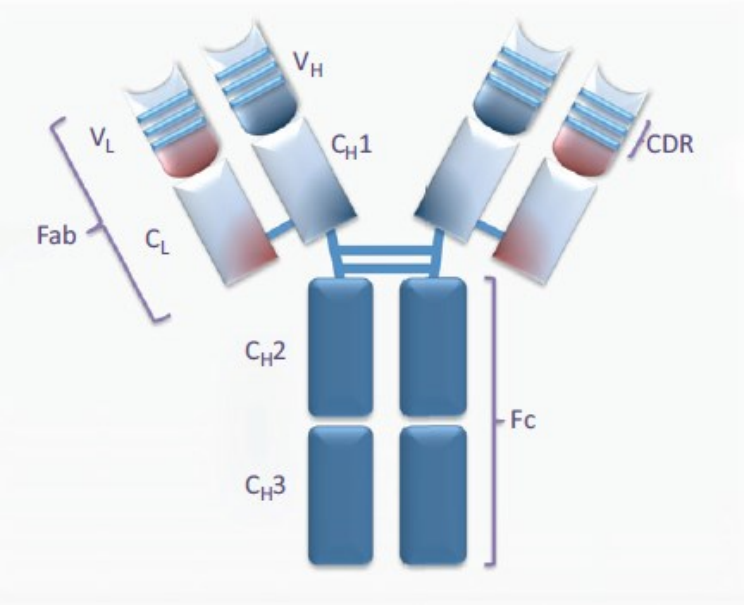
Monoclonal antibodies are a type of protein made in the laboratory that can bind to substances in the body and according to Kohler et al. (1975), they have been first described in their in vitro production of murine mAbs from hybridomas. This event has established the first step towards the development of human mAbs as therapeutics.

Since than, the rate of sales in this sector has increased dramatically: according to Ecker et al. (2015), in fact, in 2013 global sales revenue for all monoclonal antibody products was nearly $75 billion. Moreover, in the last five years the market has doubled in size as long as Since 2013, 31 new mAbs have been introduced creating a global market of a total of 57 mAbs and 11 biosimilars in clinical use by the end of 2017 (Grilo et al., 2019).

As for Buss et al. (2012), the mAbs therapy covers different fields and has lots of therapeutic applications such as allergy, asthma, cancer, and other diseases. The spread of this therapy is linked to the fact that monoclonal antibodies present advantages as high specificity, high affinity and limited side effects. Antibodies (Abs) are glycoproteins that belong to the family of immunoglobulin (Ig) kept in the B cells with the aim of recognizing and counteracting foreign organisms and antigens. Antibodies have the shape of a Y and are made up of two identical heavy chains and two identical lights chains, held together by disulphide bonds, divided

according to the different isotypes. Monoclonal antibodies, indeed, are related to the g-immunoglobulin (or IgG) isotype. The heavy chains contain a variable domain (VH), a hinge region and three constant (CH1, CH2 and CH3) domains. The light chains contain one variable (VL) and one constant (CL) domain. As can be seen from Fig 1, the parts that are connected to the antigen (a toxin or other foreign substance, which induces an immune response in the body) can also be described as variables called Fragment Antigen Binding domain (Fab). The Fab region is placed on the higher part of the Y structure and it is composed of one constant and one variable domain of both the light (VL and CL) and the heavy (VH and CH1) chain. In the lower part of the mAbs structure there is the fragment crystallizable (Fc) domain, which is, in turn, composed of two constant domains (CH2 and CH3). Moreover, the domains considered variable can be divided into hypervariable regions (or complementarity-determining regions [CDR]) which bind to the antigen directly and to framework regions (which allows the CDR to contact the antigen) (Fig 1).

Fig 1: Example of mAbs structure



Source: Buss et al., 2012.

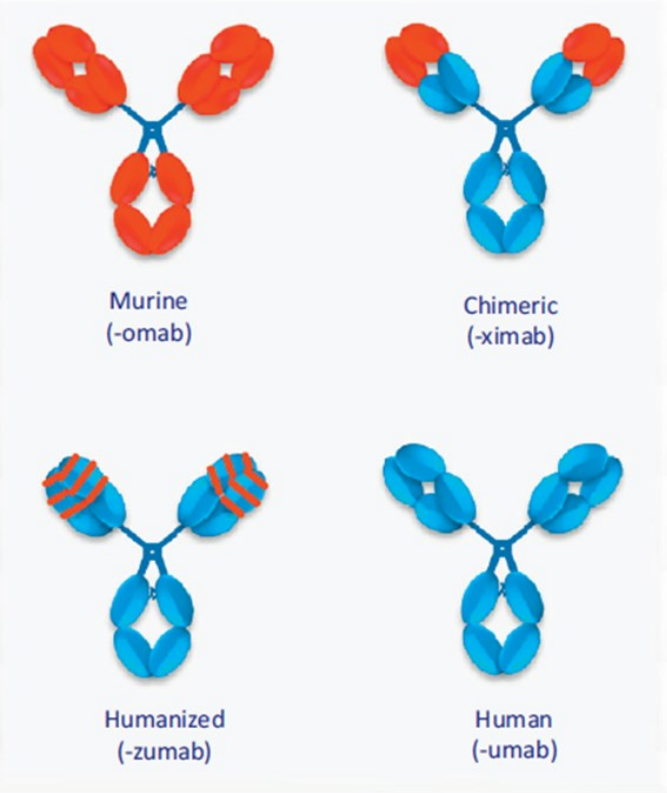
In nature, the immune response to an antigen or organism is polyclonal. It means that they are considered a set of antibodies, produced by different clones of B cells, which each recognize a different epitope (a specific part) of the molecule. However, in 1975 Kohler and Milstein described the production in vitro of murine mAbs in which Abs are completely made up from murine molecules. During the years, there had been developments in the fields and new researchers have introduced other types of mAbs (such as chimeric mouse-human antibodies and humanized mAbs) were developed, leading the way to the fully human mAbs (Ascoli et al., 2018).

Each type of monoclonal antibody can be traced back to its molecular characteristics of origin by looking at the suffix: for example, -omab, indicates that the molecule of origin is that of mice; -zimab indicates the chimeric one; -zumab indicates the humanized and –umab the human accordingly (Fig 2).

The chimeric mAbs are created from the crossing of murine antibodies in the variable region (the one that have to recognize the antigen) with the constant region of a human antibody. In this way, a human antibody is obtained with a 70% of human molecule. In addition, if the murine variable region is inserted in human antibody, the result will be a humanized antibody for 95%. In the end, thanks to biomedical engineering, it is also possible to have 100% fully human mAbs. Indeed, mAbs are currently generated by isolating or transforming antibody-producing cells taken directly from immunized animals or patients, and transplanting the antibody-encoding genes of these cells into suitable producer cell lines.

As already mentioned, the therapeutic applications of mAbs are various. From cancer to transplantation and autoimmune diseases, mAbs are also used to control infectious diseases, such as malaria, influenza and HIV for which it is possible and appropriate to use those who are termed Broadly Neutralizing Monoclonal Antibodies, dispensed individually or in cocktails (Buss et al., 2012).

Figure 2: Monoclonal antibody types and nomenclature



Source: Buss et al., 2012.

1.2 SARS-COV-2

At the beginning of December 2019 a new virus has appeared in the district of Hubei, China, more precisely in the City of Wuhan. Earlier studies reported that many primary pneumonia cases were associated with the products sold in the Seafood Wholesale Market in Wuhan. This market is a large place in an area of

50,000 m2, where seafood, fresh meat, perishable goods, and a wide variety of wildlife are sold for consumption.

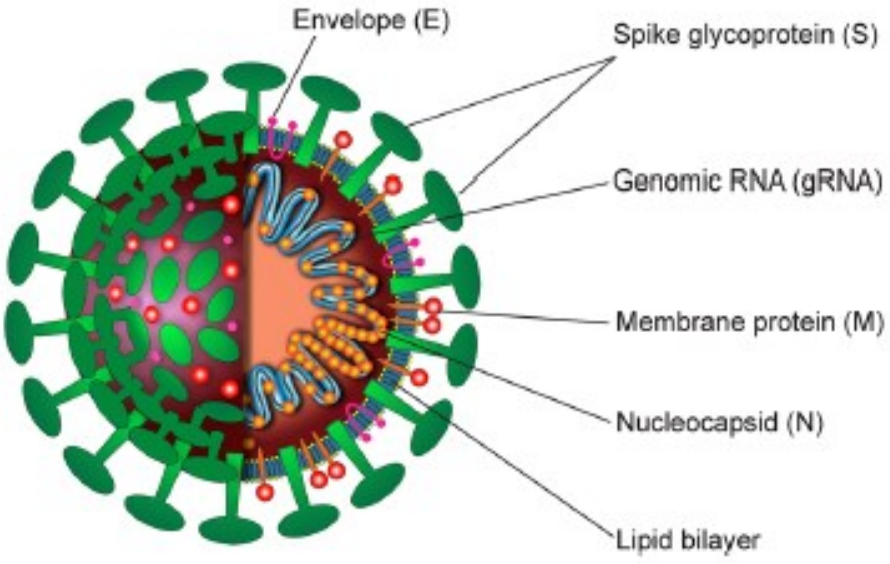
Although this virus shares 79.5% of the genetic sequence with SARS-CoV and possesses 96.2% homology to a bat coronavirus, we can consider it a new type of virus now formally known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2). In the following months, the disease reached other countries around the world and the 12th of March 2020, the World Health Organization (WHO) officially declared it a global pandemic. According to data from the World Health Organization[1], more than 173 331 478 cases of SARSCoV-2 have been confirmed worldwide, with a total of 3 735 571 deaths (9th June 2021).

SARS-CoV-2 is described as human coronavirus member of the Coronavidae (Cov) subfamily of the Coronavirinae family, which belongs to the order of Nidovirales. The Coronavirinae subfamily is further classified into four Alpha, Beta, Gamma, and Delta groups with the first two of which infect mammals, and the second two infect birds. All coronaviruses are spherical, polyhedral viruses. However, Beta coronaviruses are enveloped, single stranded RNA viruses usually found in bats and wild birds, which can evolve to infect humans and non-human mammals and birds. SARS-CoV-2 belongs to Beta genus (Beig Parikhani et al., 2021).

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019

According to the Authors, coronavirus disease 2019 (COVID-19) is the disease syndrome that the SARS-CoV-2 virus triggers and it contains four structural proteins that are encoded by Open Reading Frames (ORF). The envelope of the virus is composed of two structural proteins: E and M. The E protein is known as the coat protein and plays a role in the assembly, release, and pathogenesis of the virus. The M protein forms the virus and strengthens the curvature of the membrane and attaches to the nucleocapsid. Moreover, the protein N is linked to the viral RNA while the S glycoprotein (also known as Spike protein) connects with the receptor of the target cells facilitating the penetration of the virus into them (Fig 3).

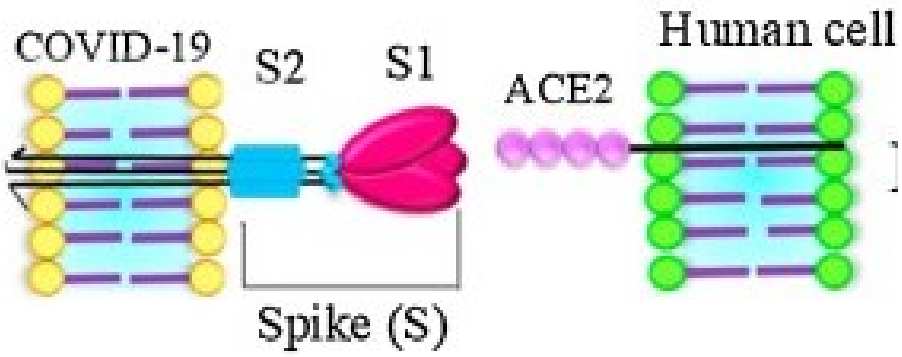
Fig 3: SARS-CoV-2 structure and its structural proteins.



Source: Beig Parikhani et al., 2021

Similarly to the past SARS-CoV, this new virus attaches to the Angiotensin-Converting Enzyme 2 (ACE2) receptor. In addition, the S glycoprotein has two subunits S1 and S2 that, once transported to the surface of the virus, have different objectives. The N-terminal S1 segment contains a signal peptide and the receptor binding domain (RBD) that interact with the host cell receptor. While, the S2 segment, anchors the S glycoprotein to the viral membrane and mediates the fusion of the viral membrane with the plasma membrane of the target cell. Indeed, studies have shown that COVID-19 through ACE2 receptor binds to human epithelial cells using ACE2 as its receiver to the host (Jahanshahlu et al., 2020) (Fig 4).

Fig 4: How Spike glycoprotein binds to human cell



Source: Razaei et al., 2020

The risk connected to the transmission of Covid19, as the majority of the coronaviruses, is linked to factors such as the host immune system, host receptors,

proliferation rate and the rate of virus mutation. As a matter of fact, this virus lives through the cells of other organisms in order to survive and to reproduce. For this reason, to replicate, Covid19 needs to enter and bind to the host cell, to translate the virus, to transcript the genome, to replicate, to translate the structural proteins and to release the virus.

The proliferation of the virus can lead to asymptomatic patients or situations of mild or even severe symptoms. This new zoonotic form could also be lethal for humans due to the invasion to the lower respiratory tract and could cause acute bilateral pneumonia. For this reason, Covid-19 represents one of the main concern during the last months since it is putting the sanitary systems of all the countries under severe pression (Jahanshahlu et al., 2020).

1.3 MONOCLONAL ANTIBODIES THERAPY FOR SARS-COV-2

Nowadays thanks to the adaptability and flexibility of mAbs, humanized and human antibodies has reached a wide range of therapies in different types of pathologies and diseases. With the increasing number of cases due to the SARS-CoV-2, several therapies and medical approaches have been tested and developed. Also, thanks to the emergency use authorization (EUA), mAbs are now considered as one of the possible weapons useful to save lives.

In the case of SARS-CoV-2, monoclonal antibodies can interact with the virus in different ways. Firstly, they could attach to one particular substance, which will stop and prevent some mechanisms linked to the spread of a disease in the human body, providing an efficient therapeutic intervention. In addition, antibody binding opsonizes the infected cells for phagocytic uptake. If viral proteins are intercalated into target cell membranes during viral egress, monoclonal antibodies can facilitate target cell death via complement fixation and membrane attack complex (MAC) activation or antibody-dependent cytotoxicity. These mechanisms may result in apoptosis or necrosis of the infected cell. In fact, mAbs can be used as immunosuppressive agents to stop and restrict the damage, reducing morbidity (the condition of suffering from a disease or medical condition) and mortality (Jahanshahlu et al., 2020).

In case of SARS-CoV-2, mAbs can decrease the viral load interfering with the virus, which is entering a cell. They manage to do that, connecting with the S protein and constraining virus attachment to cell surface receptors making the binding sites of host cells unavailable for the virus.

As already mentioned, coronaviruses infect host cells entering through the Spike (S) glycoprotein, which plays a pivotal role together with the Angiotensin-Converting Enzyme 2 (ACE2) receptor. ACE is found on cells in the respiratory system, gastrointestinal tract and endothelium and is described as a transmembrane protein. Indeed, ACE2 serves as the main entry point into cells for some

coronaviruses binding to the Spike protein. At this point, the antibodies are responsible to attenuate the interaction of the S glycoprotein with ACE2 and neutralize the infection. In this way, they can prevent the virus from binding and fusing with the target host cell, since they identify the S1 fragment and they block the interaction between the receptor RBD and the ACE2 receptor. In order to create and derive neutralizing mAbs targeted to the RDB of the S protein, scientists and researchers have used humanized murine technology or convalescent plasm from recovered patients (Taylor et al., 2021).

1.3.1 CLINICAL USE IN COVID19

Clinical trials have shown that certain types of mAbs or combinations of them used during the virus infection, could help patients in a favourable way (Taylor et al., 2021). Those mAbs were at first Bamlanivimab, Bamlanivimab together with Etesevimab created by the pharmaceutical firm Eli Lilly and Casirivimab with Imdevimab from the firm Regeneron/ Roche. However the use of Bamlanivimab alone as a monotherapy is no more accepted and will be discussed in details later on.

As for Taylor et al. (2021), antivirals are more effective when dispensed in the early phases, within hours or, at least, few days following symptoms. Furthermore, results showed that patients need to be treated as early as possible to maximize the

chance of altering the disease trajectory and promote recovery, since, according to data, the majority of patients admitted in hospitals have at least one co-morbidity. Despite this, there exist also patients without co-morbidities that have become critically ill. It follows that the lack of comorbidities will not exclude the possibility of high risk of severe disease.

In addition, Authors also proposed other ways to identify possible patients for neutralizing mAbs. One of them is the classification of people who have poor antiviral responses, such as elderly or immunocompromised patients, or through the recognition of poor T cell or B cell function. T cells are part of the immune system and focuses on specific foreign particles while B cells produce antibodies, which bind to antigens and either block viruses and bacteria from entering cells or trigger additional immune defences. For this reason, the lack of those two cells could represent a characteristic for patients' identification. However, this type of process could represent a significant impediment to the timely identification of the most appropriate patients (Taylor et al., 2021).

CHAPTER 2: PATENTING PROCESS AND ITS REGULATION

2.1 INTRODUCTION TO INTELLECTUAL PROPERTY AND PATENTS

Intellectual property (IP) refers to the human creation and its main purpose is to encourage the creation of intellectual goods giving property rights to people through the application of rules and laws. As for Besen et al., (1991), the objective of this protection is to incentive people and firms to maximize the difference between the value of the intellectual property that is created and used, and the social cost of its creation, including the cost of administering the system. In fact, according to Authors, due to this type of protection, producers are stimulated to invest money in innovation only if they receive an appropriate return. Whether producers will have the correct incentives depends on their ability to appropriate at least some of the value that users place on those works. If potential innovators are limited in their ability to capture this value, they may not have enough incentive to invest a socially optimal amount in innovative activity.

For this reason, Intellectual Property Rights (IPR) arise and allow creators to execute their rights over their work for a set period of time. Those rights include copyright, trademarks, patents and many others. IPR allow people to produce socially desirable innovations in which people probably would not have put resources, without some guarantee of private ownership, as their findings would rapidly be imitated, leaving them with no profit. (Greenhalgh et al., 2007)

In particular, a patent is a document, issued by an authorized governmental agency, granting the right to exclude anyone else from the production or use of a specific new device, apparatus, or process for a stated number of years. (Griliches Z., 1990)

2.1.1 PROS AND CONS OF PATENTS

The patent right is one of the most powerful mean in the intellectual property system and it represents an innovation incentive and a protection instrument. As for Malerba F. (2000), the analysis of the patent strategy should take into consideration two aspects. On one hand, patent avoids indiscriminate exploitation by competitors of the discoveries together with the research carried out by the innovating company. In absence of such a protection mechanism, anyone has the opportunity to exploit commercially the results of other people's research activities. On the other hand, patents advertise and share information regarding the innovation, since it is a public document. Through the citations of a patent by other patents it is possible to have an evaluation of its quality and importance. Moreover, patent citations provide an idea of its reliance on scientific progresses.

In fact, according to the Author, patents are considered an innovative output indicator, even if analysis have demonstrated that there exists a possibility that the patent request is demanded in the earliest phases of the innovative process. In this way, patents could represent an inventive output indicator since many patented products do not reach the commercialization phases.

However, the Author proceeds the analysis with the idea that the patent should also be understood as a signal of the technological ability of a firm in a particular technology. Indeed, the patent request means that the firm is able to use a particular technology and that is moving towards that goal. Patents are the instruments through which the industrial property is directly protected while the research is encouraged indirectly. In other words, patents also represent a legal entry barrier for the business competitors, creating temporary monopoly.

2.1.2 PATENTING PROCESS IN EUROPE

The introduction of patent protection helped many companies in planning the cost-effectiveness of investments made in R&D in fact, obtained the patent, its owner is allowed not only to sell the product, but also to prohibit anyone else from doing so, without having obtained his authorization, for instance, through the use of a license. The European one is a single procedure for examining the patent title which afterwards concession, may be validly extended to all Contracting States. The European procedure is activated by filing a patent application in accordance with the formal and qualitative standards defined by the European Patent Convention, at the European Patent Office (EPO), and requesting a merit examination of the invention (EPO, 2020).

As stated by WTO[2], an important role in defining a regulatory framework at the international level reference for patents is carried out by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS is an international agreement that has established the minimum standards of intellectual property protection, to which they must comply with all the countries that, having signed this treaty agreed to introduce and enforce chemical and pharmaceutical patent protection. Another important step of this agreement concerns the harmonization of the duration of patent protection, which is twenty years from the date of filing the application, provided that the owner pays an annual fee for its maintenance.

According to art. 52 of the European Patent Convention [3], European patents are granted for inventions in any technological field, provided that fulfil some characteristics that are explained in the following articles:

a) Novelty, *"An invention is considered new if it is not included in the status of technique "*(art. 54). The state-of-the-art means everything that has been returned accessible or disclosed to the public, anywhere in the world, prior to the date of filing the patent application, by any means of dissemination.

[2] https://www.wto.org/english/tratop_e/trips_e/trips_e.htm

[3] Convention on the Grant of European Patents (European Patent Convention) of 5 October 1973. Revised by the Act revising Article 63 EPC of 17 December 1991, and the Act revising the EPC of 29 November 2000.

b) Inventive, *"An invention is considered as implicating an inventive step if, for a person in the trade, it is not in a way evident from the state of the art "*(art. 56). The evaluation of the inventive step is less objective compared to the novelty one. Therefore, it is also more difficult, because it is necessary to examine the state of the art, the average level of knowledge of the expert in the field together with the possible existence of motivations and incentives to move in the direction of the invention.

c) Suitable for industrial application, "*An invention is considered suitable to have an industrial application if its object can be manufactured or used in any kind of industry, including agriculture*" (art. 57). The invention must be useful in industry, so this requirement coincides a lot often with the simple concept of utility.

d) In addition, it must be described clearly enough, in such a way it must be reproducible.

Once fulfilled those characteristics, the request should be handed to the competent authority, which could be a national patent office or EPO in Europe. The request needs to be made up of some elements, that are: the title that corresponds to the object of the invention; the summary in which is explained the invention; the official description made up of a clear and complete definition so that the problem and the solution can be understood; the claims regarding the demanded object to be patented and protected; and the drawings, if needed.

By filing the application in a member state of the Paris Convention for the Protection of Industrial Property[4] , the owner has a priority right of 12 months to file the application in other member states. The application is published 18 months after the filing date. Following the examination of the formal requirements of the application, the verification of prior art and the patentability requirements, the patent can be granted or refused.

After the granting of a patent, a possible opposition procedure by third parties may take place. The patent has national value, in fact the European patent consists of a bundle of national patents. There is also the possibility of applying for an international patent (at a national patent office, EPO or World Intellectual Property Organization), in accordance with the Patent Cooperation Treaty (PCT)[5] Convention, through a centralized filing procedure. It provides for a preliminary examination of the existence of the patentability requirements. Following a positive opinion, a patent application can be filed nationally in the individual States of interest, within 30 or 31 months from the filing date (or priority).

[4] The Paris Convention, concluded in 1883, was revised at Brussels in 1900, at Washington in 1911, at The Hague in 1925, at London in 1934, at Lisbon in 1958 and at Stockholm in 1967, and was amended in 1979. The Convention is open to all States. Instruments of ratification or accession must be deposited with the Director General of WIPO.

[5] The Patent Cooperation Treaty was signed on the last day of the conference on 19 June 1970. The Treaty entered into force on 24 January 1978, initially with 18 contracting states. The first international applications were filed on 1 June 1978.The Treaty was subsequently amended in 1979, and modified in 1984 and 2001.

2.1.2 PATENTING PROCESS IN THE U.S.

In U.S,, to obtain a patent the proponent needs to fulfil a request at the US Patent and Trademark Office (USPTO). The first American law regarding this topic goes back to 1970, however the most recent one is the Unites States Patents Act of 1952[6] with a section dedicated to patents in the Title 35 of the United States Code. One of the most relevant transaction in the Leahy-Smith America Invents Act (AIA)[7] is the shift from the "first to invent" principle to the "first inventor to file". In this way, the date of the invention is irrelevant, what is important is the date of the inscription to the USPTO.

According to ICE (2016), this country allows different types of patents, such as the most common one, called the utility patent, the design patent or the plant patent. The Utility patent is issued to whoever has invented or discovered the following four types of inventions: (a) a process, (b) a machine, (c) an artifact or (d) a composition of matter (provided that they are new, useful or constitute an improvement of existing products). The design patent is inherent in the drawing's ornamental, i.e. the shape of an artifact (not its structural aspects or functional). Finally, the plant patent grants specification protection of the invention or the

[6] Subject to numerous amendments over the years, the Act originally divided the patent law into three parts: Part I- Patent and Trademark Office; Part II- Patentability of Invention and Grant of Patents; Part III- Patents and Protection of Patent Rights. A later amendment added Part IV- Patent Cooperation Treaty.

[7] Its central provisions went into effect on September 16, 2012 and on March 16, 2013.

discovery and reproduction, in an asexual manner, of a new and distinct variety of seed or plant.

Moreover, Authors specify that patent request could be provisional or non-provisional. The provisional one is not examined for the purposes of its patentability, as its function is only to guarantee the determination of an exact date registration for recognizing patent rights. Since the provisional one lasts 12 months, by that period, the inventor should fulfil the request for the non-provisional request in order to receive the real patent. In addition, in this case, the inventor needs to adhere to a format, which includes a specification, application, drawings and an official statement. Once the Office receives the request, the examiner assigned to the case, carries out an investigation either formal or technical-legal. In particular, he or she conducts an independent research on the state of the art in the specific sector indicated by the inventor about the elements of the invention. At this point, the examiner evaluates the application in its technical aspects, verifying that the legal requirements are met. The results of the procedure may be different: the Office could reject the patent application or ask for clarification. In each case, within 18 months of filing, the application will be published. If the examination is successful, the USPTO will send the applicant a Notice of Allowance, together with the form for the payment of registration fee to be made within 3 months of receiving the letter. Failure to pay the fees is equivalent to the abandonment of the patent.

Furthermore, patents filed starting from 8 June 1995 have a duration of 20 years from the date of filing of the application (this applies to utility patents and plants patents). The same rules apply to requests submitted for the procedure referred into Patent Cooperation Treaty (PCT). The duration of the patent for ornamental designs is 14 years old.

2.2 PATENTS IN PHARMACEUTICAL SECTOR

The pharmaceutical sector is a major user of the patent system. While only a small - and declining - number of new chemical entities are approved annually, thousands of patents are applied to protect variants of existing products, processes of manufacture or, where admitted, second indications of known pharmaceutical product. (Correa, 2007)

According to Notarbartolo et al. (2009), In recent decades, research in the biomedical sector has been mainly conducted by the pharmaceutical industry. Consequently, it is understandable the need to protect the drugs investment made with a patent in order to prevent exploitation from competitors in the sector. In particular, in Italy, drugs have been patentable since 1978. Authors have affirmed that the pharmaceutical companies can rely on different types of patents:

- Product patent: determines the protection of a specific active ingredient of synthetic or natural nature. The new compound must be defined through the general structural formula, which must be as broad as possible. The product

patent guarantees a monopoly on all uses and all processes applicable by analogy to the new product, without an obligation to prove its effective reduction in practice. The companies opt for this type of patent when the synthesis process turns out to be very complex and difficult to imitate and is generally believed to be the most effective among the various types of patents. In particular, the product patent could be of two type: barrier patents or selection patents.

- Process patent: it is a kind of protection for the inventors for a certain process of creating or manufacturing a product. The protection grant is for a particular manufacturing process and not for the product itself. One may produce the same product with some other process or by simply altering various parameters of the method. It protects only a particular synthesis process of one certain molecule. This patent can be applied if a patent does not cover the molecule studied, or if you own the patent. In case companies opt for the process patent, the characteristics of the drug would be disclosed, giving competing companies the opportunity to replicate the molecule.
- Medical use patent: it relates to a new therapeutic indication for a product that has already a demonstrated use in the medical field. The patent laws of almost all countries provide possibility to patent therapeutics, as long as it is possible to demonstrate the non-obviousness of to the previous therapeutic indication. This type of patent also responds to a logic:

guaranteeing expensive investments even for smaller companies o for activities related to the development of a drug, which do not generate New Chemical Entities (NCE) that can be patented as a product.

- Patent for synergism: if a drug A, administered in association with a drug B, produces a greater therapeutic effect than would be expected from administration of the single drugs, it is possible to patent the association. It is possible to apply for this patent only if it is does not cover the molecule studied, or if the applicant is not the owner the molecules patents.

2.2.1 DATA EXCLUSIVITY AND MARKET PROTECTION IN EUROPE

Data exclusivity and market protection are two intertwined provisions that could be added to the patent defence. To understand those provisions, it is necessary to introduce the EMA authority.

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. EMA is a networking organisation governed by an independent Management Board, which is the Authority's integral governance body. In addition to its supervisory role, it also has general responsibility for budgetary and planning matters, the agenda of the Executive Director and the

monitoring of the Agency's performance. As reported by EMA[8], Members of the Board are selected to guarantee the highest levels of specialist qualifications to cover the broadest possible geographical spread within the EU. It is made up of one representative of each EU Member States, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations. In addition to these, the Management Board also has one observer each from Iceland, Liechtenstein and Norway.

The representatives of the Member States, European Commission and European Parliament are appointed directly by the Member State and institution concerned. The four 'civil society' Board members (patients', doctors' and veterinarians' representatives) are appointed by the Council of the European Union, after consultation of the European Parliament. The charge of the Board lasts for three years and can be renewed.

Regarding the data exclusivity and market protection, the Article 14 (11) of Regulation (EC) No 726/2004 states:

" (...) medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten year period of marketing protection, in which connection

[8] https://www.ema.europa.eu/en/about-us/who-we-are#management-board-section

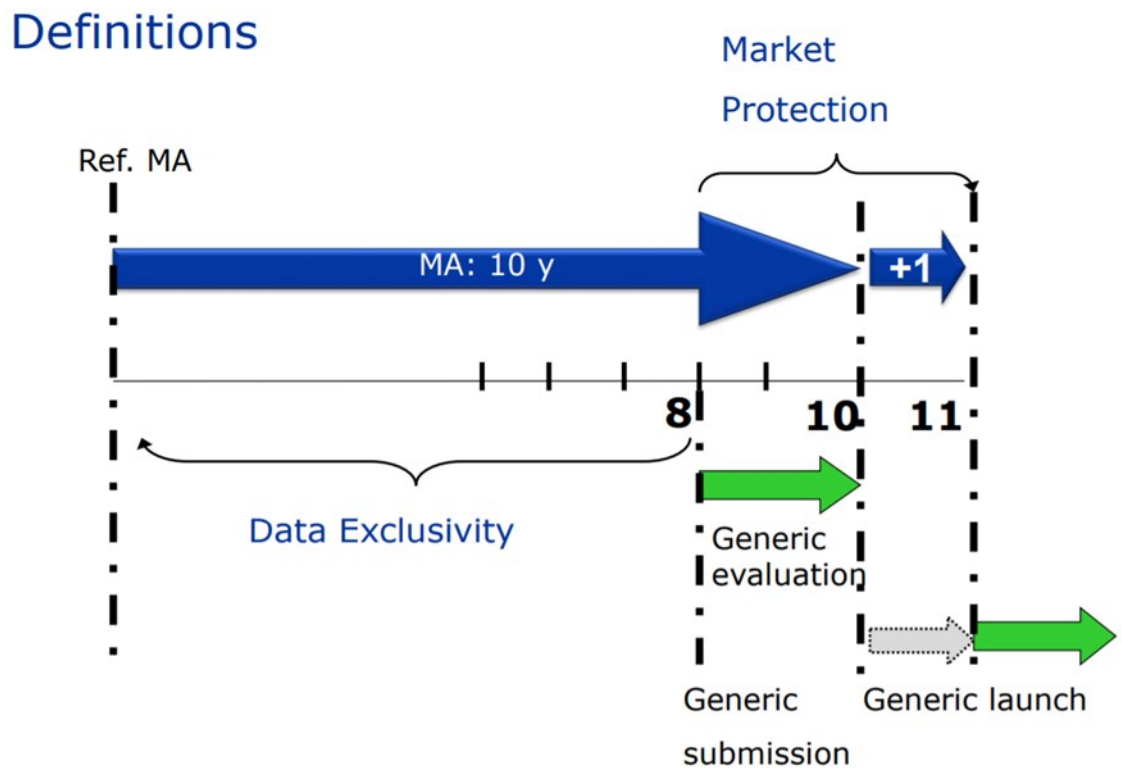
the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies."

In other words, according to EMA[9], data exclusivity is the eight years period from the initial authorisation of a medicine, during which the marketing-authorisation holder benefits from the exclusive rights to the results of preclinical tests and clinical trials on the medicine. After this period, the marketing authorisation holder is obliged to release this information to companies wishing to develop generic versions of the medicine. Market exclusivity refers to the 10-year period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market. After the 8 years have expired, a generic company can make use of the pre-clinical and clinical trial data of the originator in their regulatory applications, but still cannot market their product. After a period of 10 years from the grant of the innovator company's marketing authorisation, the generic company can also market their product, unless the innovator product qualifies for a further one year of exclusivity. This additional 1 year may be

[9]https://www.ema.europa.eu/en/documents/presentation/presentation-data-exclusivity-market-protection-orphan-paediatric-rewards-s-ribeiro_en.pdf

obtained in several circumstances, such as where the innovator company is granted a marketing authorisation for a significant new indication for the relevant medicinal product. In such a situation the generic company can only market their product after 11 years from the grant of the innovator company's marketing authorisation (Fig. 5).

Fig 5: Data and Market exclusivity timeline



Source: EMA, 2018.

2.2.2 REGULATORY EXCLUSIVITY IN USA

First, in USA the drugs authorization and protocols of therapies must be approved by their national regulatory Agency, which is the Food and Drug Administration (FDA). As stated by FDA[10], it is a federal agency of the Department of Health and Human Services, which is responsible for protecting and promoting public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

According to the FDA, the United States Congress has provided exclusive rights, which operate outside the context of patents, for certain types of drugs, in order to control the timing of barriers to entry of a regulatory nature. Sometimes the exclusive rights protect the product at the same time as the patent, and at other times extend the term of it. There are four types of exclusivity that fall under the Non-Disclosure Agreement (NDA) statutory requirements:

- Orphan Drug Exclusivity (ODE): orphan drugs are granted a period of exclusivity equal to seven years starting from the approval of an NDA or a Biologics License Applications (BLA), and deny the FDA the ability to

[10] https://www.fda.gov/about-fda/what-we-do

approve other claims for the same type drug or for the same "orphan disease" for seven years. It is regulated by the Orphan Drug Act[11].

- New Chemical Exclusivity (NCE): applied to drugs that do not contain active parts already approved by the FDA, they are guaranteed five years of exclusivity starting from the approval of the request.
- Other exclusivity: drugs are granted when the request for approval contains a report indicating new clinical investigations (other than bioavailability) conducted or sponsored by the applicant and essential for approval, for a period of three years.
- Paediatric Exclusivity (PED): the Food and Drug Administration Act adds six months of exclusivity at the end of the term of existing patents or other exclusivities, for rewarding paediatric drug testing. To get this exclusivity the FDA requires that paediatric studies to be provided regarding the drug.
- 180-Day Exclusivity: FDA may also grant exclusivity to abbreviated new drug applications (ANDAs) for generic drugs. Under the Drug Price Competition and Patent Term Restoration Act, or the Hatch-Waxman Act, a company can seek approval from FDA to market a generic drug before the expiration of a patent relating to the brand name drug upon which the

[11] An Act to amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes. Enacted by the 97th United States Congress and effective from January 4, 1983.

generic is based. The first company to submit an ANDA with the FDA has the exclusive right to market the generic drug for 180 days.

2.2.3 PATENTS REGULATION FOR MABS

As for Germinario et al. (2018), antibodies and the substances derived from them, have been patented for decades; however, obtaining patent protection for these inventions could represent a challenge for the experts involved. In fact, antibody applications are of great interest due to their potential applications in the fields of immunotherapy and diagnostics. Their use, above all those of mAbs, are a result of antibodies' ability to bond with an epitope on the surface of an antigen. This key characteristic is a determinant aspect in the patent process of an invention involving antibodies.

In the design of a patent, especially for mAbs in therapeutic use, Authors have categorized four general aspect to keep into consideration:

1. The patentability of proteins: since the antibody is a complex protein, by definition, is a patentable biotechnological invention according to the articles of the European Patent Convention[12]. In this case, an antibody is identified a mean of its structural or functional characterization.
2. The structural or functional characterization of the object to be patented: as for all types of proteins, antibodies need to be recognized according to the

[12] According to the provisions of EPC Rules 26–30.

structural characterization of a particular amino acid sequence (or partial sequence) or through the oligopeptide sequence of the complementarity-determining regions (CDRs) that enable the antibody to recognize an antigen. Indeed, the most common approach is the functional characterization of antibody to recognize and bind selectively to a specific antigen or, in the case of mAbs, to a specific antigenic site of a protein.

3. Selection inventions: it could also happen that from a larger family of antibodies, a specific one is chosen to be patented. This selection is possible if the subgroup or the selected element causes a technical effect that had not been previously recognized and described since it is possible that those antibodies present a new characteristic.
4. Inventions of therapeutic applications: it derives by the particular bond created with a specific antigen that allows a pharmacological action that be of therapeutic utility.

As already stated, a mAb is able to recognize a single epitope on the surface of an antigen, which distinguishes it clearly from a generic polyclonal antibody. However, according to Authors, this aspect is not enough to receive a patent since it could happen that the process does not involve an “inventive step”. Instead, it could be patented if, it proves useful for producing a therapeutic response, provided the effect produced is not obvious (for the purposes of patentability).

Patentability criteria differ from case to case, but as for any other invention, the one based on the selection of a specific antibody has to meet the disclosure requirement that is being described, or disclosed, in a "sufficiently clear and complete" manner. Also, the application needs to describe how the antibody is produced and, in case of hybridoma-derived mAbs, the hybridoma in question must be deposited with an officially recognized depositary institution with microorganism-storage facilities. In fact, according to the Rule 31 EPC, the patent description has to be integrated with the deposit of the microbiological material when it implies a microbiological procedure that is not accessible to the public. Moreover, in case of a claim of a pharmacological effect, the application must insert the results that report evidences. Due to the huge variety of possibilities through with an antibody can be defined, starting from the structural characteristics, the functional ones or though the therapeutic activity, Authors have decided to provide some cases, in which the eight different possibilities of antibodies patentability are summarized (Table 1). In case 1, a new antigen and an antibody are described for the first time so it can be patented without the need of further characterization. In case 2 the antigen is known; however the inventive factor of the antibody is respected since it shows a certain level of specificity or has a new and non-obvious function. In case 3 the antigen is known but the selected antibody respects the characteristic of novelty because is defined in terms of specific properties and not generic ones. In case 4, with a known antigen, the antibody is patentable since it is already known for a use other than a

therapeutic use, and thus can be patented on the basis of a claim based on its first use as a medical agent. In case 5 the antigen is known together with the polyclonal form of the antibody, so the antibody is patentable in case it is a monoclonal one and if it has a novel and non-obvious function. In case 6, the monoclonal antibody could be patented only if it shows a different specificity and another functionality. In case 7 the only possibility for a patent protection would be if it characterized in a very precisely way for instance though the CDR sequences. Lastly, in case 8 patents are allowed in situation of novelty of fragments and new functionality since they could have a better efficacy and safety profile.

Table 1: Cases of rules governing antibody patentability

	Antigen	**Antibody**	**Patentability conditions for a second antibody**
Case 1	Not known	Not known	(Newly discovered antigen) Novel: yes, even in the generic form An inventive step: yes (usually).
Case 2	Known	Not known	Novel: yes An inventive step: yes, if it has particular features(binding specificity, non-obvious function, etc).
Case 3	Known	Known in the generic form	Novel: yes, if selected by functional or structural characterization. An inventive step: yes, if is exhibits a new, non-obvious function.
Case 4	Known	Known for use in technical analyses	Novel: yes, if for a first (or subsequent) therapeutic application An inventive step: yes, if the therapeutic application is non-obvious.
Case 5	Known	Known in the generif or polyclonal form	Novel: yes, if it is a monoclonal antibody with different specificity. An inventive step: no if it just has the properties of all mnoclonal antibodies; yes, if it has a novel and non-obvious function (e.g. cytotoxicity, apoptosis).
Case 6	Known	Known in the monoclonal form	Novel: yes, if it is a monoclonal antibody with different specificity. An inventive step: depends on functionality.
Case 7	Known	Known in the generic monoclonal form	Novel: yes, if characterized very precisely (e.g. giving the CDR sequences) An inventive step: depends on functionality.
Case 8	Known	Known	Novel: yes, if an antibody fragment An inventive step: depends on functionality.

Source: Germinario et al. (2018)

2.3 REGULATION OF DRUG INTRODUCTION IN THE MARKET

Once the problems of the property rights are overcome. and having analysed the issue of the patents in different countries, pharmaceutical companies should follow procedures to be allowed to introduce a drug in the market.

In those stages, the documentation concerning the production process together with the information on the quality and the results of the clinical trials, must be included in order to demonstrate the authorities the safety and efficacy of the new drug. In case of approval, the drug can be placed in the market and used by patients.

In addition, the law provides that even after the market placement of the new drug, Authorities will monitor it in order to detect side effects and problems that may have been missed during previous clinical tests under special conditions. To do that, further studies are carried on, concerning incidence and the severity of adverse drug conditions, cost-benefit analyses and investigation regarding the patients' quality of life, and so on. Pharmaceutical companies need to follow principles and regulation stated by competent Authorities in order to better allocate the resources. Those resources are needed to face challenges that have a significant financial impact on those companies.

2.3.1 EUROPEAN REGULATION FOR DRUG INTRODUCTION IN THE MARKET

The drug introduction in the European market is subjected to some regulatory steps. As for Kashyap et al. (2013), pharmaceutical companies must submit a request to the regulatory authority, in order to obtain the commercialization approval. As reported by European Medicines Agency[13], this phase is called *Marketing Authorization Application (MAA)* and is directly submitted to them. Regarding the process for the approval of drugs for commercialization, it can follow different paths:

- It could be a centralized procedure, which is mandatory for products deriving from biotechnologies, orphan drugs and for drugs used for some specific diseases, such as AIDS, cancer, diabetes or neurodegenerative diseases. The request is made directly to the EMA and leads to the release of the sale authorization in Europe by the Commission, which is mandatory for the future commercialization in all member states.
- The mutual recognition procedure, applicable to traditional drugs and based on the recognition of an existing authorization by other member states.
- The decentralized procedure, through which the request for sale authorization is submitted simultaneously in several member states, one of which

[13] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation

is chosen as the reference member state. At the end of the procedure, the authorization is issued in the reference state and the related ones.

Each request should be done according to specific forms, called Common Technical Document (CTD). It shows information such as the name, quality and quantity of the ingredients, the production methods, the therapeutic indications, the date of expiry, the collateral effects, the environmental risks and the clinical results.

The EMA's committee entitled to give an opinion regarding these information and the relative authorization to commercialization is the Committee for Medicinal Products for Human Use (CHMP), which send its opinion to the European Commission, who takes the final decision after a consultation with member states. After the release of the approval, the company has to carry out risk-benefit analyses of the product to ensure compliance with good manufacturing practice (European Commission, 2009).

2.3.2 US REGULATION FOR DRUG INTRODUTION IN THE MARKET

United States are considered one of the most demanding country to approve new drugs (Kashyap et al., 2013). In USA the drug introduction phase is known as the *registration* and it is submitted to the Food and Drug Administration (FDA). As for FDA[14], it corresponds to the *New Drug Application (NDA)* in case of traditional

[14] https://www.fda.gov/drugs/how-drugs-are-developed-and-approved/types-applications

drugs, or *Biologic License Application (BLA)* in case of biopharmaceuticals. According to the Federal Food, Drug & Cosmetic Act (FDCA[15]), before the approval, the Authority needs the demonstration of the safety and efficacy of the drug itself. During the preclinical research phase, FDA requires companies to stick to Good Laboratories Practises (GLPs) and present data together with a declaration in which it states that they have been following those principles. After this, a request known as Investigational New Drug (IND) for clinical test on humans should be made by the companies During those tests, FDA establishes which are the minim standard to be followed in documents called Good Clinical Practises (GCPs). Those practises allow FDA to control the subjects involved in the tests. In addition, once presented the NDA and BLA requests, FDA[16] states that they can analyse the results of the preclinical and clinical tests and all the relevant information. Once approved, the authority applies some regulation standards such as the advisory of adverse events, the production according to current good manufacturing practises (cGMPs), any changes in the production process and further tests to identify collateral effects.

[15]https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act

[16]https://www.fda.gov/drugs/development-approval-process-drugs/guidance-documents-drug-applications

2.3.3 MABSREGULATION FOR COVID19

As it is easy to envisage, mAbs should follow the mentioned procedures in order to be available on the market. However, due to the COVID-19 pandemic, they have been object of some extraordinary measures. European countries' governments agreed on trials results suggesting mAbs to be administered to risk-patients exposed to SARS-CoV-2. For this reason, some organisations accepted to use them with the Emergency Use Authorization (EUA). The EUA allows the temporary use of a medicine or therapy under certain circumstances, as long as emergency circumstances arise such as the pandemic one of the COVID19.

In Italy the responsible authorities for the regulation of mAbs is the Agenzia Italiana del Farmaco (AIFA). AIFA is a public body that operates independently, transparently and economically, under the direction of the Italian Ministry of Health and the supervision of the Italian Ministry of Health and the Italian Ministry of Economy.

In February 2021, the Agency has approved the use of the following mAbs: Bamlanivimab alone or in combination with Etesevimab and Casirivimab in combination with Imdevimab. These mAbs have been accepted temporarily with the Decree of the Minister of Health of 6th February 2021 published in the "Gazzetta Ufficiale" (GU) and they have been accepted on the GU of 8th February 2021, no. 32 for the treatment of mild to moderate coronavirus disease 2019 in adult and paediatric patients. The "Gazzetta Ufficiale" is the official source of knowledge

of the regulations in force in Italy. It is a tool for the dissemination, information and formalization of legislative texts, public and private acts that must come with certainty to the knowledge of the entire community. However, as reported by AIFA[17], data have shown evidences to change its decision. In fact, from the 8th of May it will not be possible to prescribe the monoclonal antibody Bamlanivimab in monotherapy, for the treatment of Covid19.

At first, also in USA the Agency approved the use of the Bamlanivimab alone or in combination with Etesevimab and Casirivimab in combination with Imdevimab. However, FDA[18] decided to revoke it on April 2021 for Bamlanivimab. The EUA suspension for the mAb Bamlanivimab has been made since some criteria are no longer met and potential benefits of that specific mAb no longer outweigh the known and potential risks for the product.

[17] https://www.aifa.gov.it/web/guest/uso-degli-anticorpi-monoclonali

[18] https://www.fda.gov/media/147629/download

CHAPTER 3: EMPIRICAL ANALYSIS

3.1 BRIEF LITERATURE REVIEW OF BIBLIOMETRIC ANALYSIS

This analysis aims to evaluate patents that address the therapeutic use of the monoclonal antibodies for the treatment of the individuals infected with the virus of the Sars-CoV-2. In order to explore those patents, an introduction to the bibliometric concepts has been developed, together with a focus of bibliometric indicators for patent analysis.

Bibliometric analysis has born due to the fact that academic knowledge and the number of articles published are increasing leading to a situation in which the knowledge is spreading across a huge number of fields and disciplines (Jinha, 2010). As a matter of fact, a methodology to study those type of information has been developed. Around 1920s some studies regarding the frequency distribution of scientific productivity and a citation-based study have been published (Gross et al., 1927). However, these attempts remained unnoticed until when some cornerstones of the bibliometric analysis, such as “Science since Babylon” and “Little science, Big Science” were published. The author was one of the first researcher to lay the foundation of modern research evaluation techniques. The increasing importance and use of the bibliometrics is strictly linked to two factors: the development of the technology during the years and the availability to reach information through the use of the internet all over the world, thanks to the use of

databases such as Web of science (WoS), Scopus or Google Scholar (Li et al., 2010).

Later on, when the first periodical called "journal Scientometrics" was launched, in 1978, bibliometrics evolved in a recognized and developed discipline with a research profile and corresponding structures. In particular, in the 1990s, bibliometrics has become a tool usually used in the research management, that can rely on citation analysis and sophisticated techniques. During the 21st century, a new indicator has been proposed by Jorge E. Hirsch, the h-index. It takes into account the publication activity and citation impact. Thanks to this index, the idea of bibliometrics shifted from a macro level to a micro level (Hirsch, 2005).

The Author describes it as:

"A scientist has index h if h of his/her N_p papers have at least h citations each and the other papers have no more than h citations each [...]."

Since it is not difficult to calculate, this index has been well received and in other extensions of the work, the author affirmed that, together with other bibliometric indicators, can be used to predict the future success of an individual. The h-index is not only easy but also it combines the effect of the number of publications and the citation rate in a balanced way. However, if on one hand, this index presents several advantages, on the other hand it shows cons too. Indeed, according to this kind of indicator, even if the author stops to be productive, the index will never decrease. In addition, it is also limited to the number of articles that are produced over a period

of time and strictly connected to the field in which the authors work. It neglects co-authorship and is influenced by self-citation. It can also show a different behavior when applied to other units than individual scientists (Norris et al., 2005).

For all the mentioned characteristics, a lot of new variants to this index have been developed. One of the most important is the g-index. As for Egghe (2006), the index is described as:

"A set of papers has a g-index g if g is the highest rank such that the top g papers have, together, at least g^2 *citations. This also means that the top g + 1 papers have less than* $(g+1)^2$ *papers."*

In other words, it defines the highest natural number g of publications that have been cited g or more times and as a matter of fact, it is higher than h-index discriminating better different citation patterns (Rubem et al., 2015). The spread of the bibliometric indicators has led to different interpretation of this methodology. As for Donthu et al. (2021), the bibliometric analysis can be performed using two categories known as 1) performance analysis and 2) science mapping.

The first one takes into account the contributors of the components of the research using metrics related to the number of publications, the citations or the combination of them, while the latter analyses the links among those components through the use of quantitative techniques.

Performance analysis uses three different categories of metrics. The first group is the one dedicated to the publications, such as the total number of publications, the

number of the authors that contribute to them, the number of publications done by a sole author or if there are co-authored projects, the period of time counted on years during which they are active and their productivity per active year. Then, among the techniques found in the performance study, there are also those metrics related to the citation, such as the total citations and the average citations. Finally, there exist also the metrics that take into account the union of citation and publication metrics. Those could be for instance, the collaboration index (described as the measure of the collaboration of each author), the collaboration coefficient (the standardized extent of the author collaboration), the number of publications cited and the proportion, the citations per cited publication, the h-index (as mentioned before, the h number of publication that are cited at least h times), the g-index (the g number of publications that receive at least g^2citations), the i-index (the number of publications cited at least i times).

Analysing the science mapping techniques, Authors mention: citation analysis, co-citation analysis, bibliographic coupling, co-word analysis and co-authorship analysis that can be enriched with a network analysis tools. They define citation analysis to evaluate the importance of a publication with the number of citations that it receives, highlighting the most influential publications in the sector of the research. Co-citation analysis is based on the idea that if publications are present together in the references several times they belong to the same theme and field of study. In this case, this analysis could lead to the discovery of important business

scholar clusters. Bibliographic coupling is described as a division done on a specific timeframe of the publications in clusters, based on the presence of shared references and considering citing publications. The co-word analysis is no more based on cited or citing publications, but on the relationships created by common words among them. The idea here is that if there are words that appear together, probably there is a connection from a thematic point of view. However, this kind of analysis has to be performed in a cautious way since words could also be extrapolated out of their context or used with a general meaning. To conclude, the co-authorship analysis considers the relationships of scholars in a research sector and studies how those people work together, since collaborations usually lead to improvements and contributions to the general knowledge (Tahamtan et al., 2016).

3.1.1 PATENT ANALYSIS THROUGH BIBLIOMETRIC INDICATORS

Bibliometric analysis is applied to patents to reach different goals, such as to study and forecast future technologies and R&D in different kind of industries, both the in public and private sector. As for Daim et al. 2006, before, bibliometrics has been utilized to study academic journal citations, nowadays it allow researchers to examine the past in order to plan the future. When bibliometrics is applied to patent analysis, it is combined with the right choice of indicators. In this way, some statistical measures are derived, which can help researchers and entrepreneurs interpreting the inventiveness of some countries, regions, firms and their

technological performance, also tracking some globalisation patterns. For these reasons, bibliometric concepts have been chosen and used in this analysis with the aim of interpreting the results obtained.

A patent contains information regarding different aspects of the invention, which are important for statistical purpose, above all in this analysis. Authors state that patents are useful resource to extrapolate information about a particular industry or technology and to forecast the new trends. That information is standardized through the different patent offices that utilize some codes. These codes are for instance the INID. The INID is the Internationally agreed Numbers for the Identification of (bibliographic) Data, and they are placed close to the information and data on the patent document. They do not vary with the languages so it is possible to understand where the information is placed in the document, even when the language is unknown.

In addition, another important standard code, is the International Patent Classification (IPC), which is an alphanumeric code that is used to indicate the technical subject of the invention and it is assigned by the office. As mentioned by WIPO[19], it is a hierarchical system of language independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain. Indeed, the technology is described using levels

[19] https://www.wipo.int/classifications/ipc/en/

of identification. At the first level there are sections indicated with eight capital letters. Each section is subdivided into classes represented with the section letter followed by two-digit number. At the third level there are the subclasses represented as the class symbol followed by a capital letter. Each subclass is broken into subdivisions or groups represented as the subclass symbol followed by two numbers separated by an oblique stroke.

The information collected in a patent can be classified into three categories, which are: 1) technical descriptions; 2) development and the ownership; 3) history connected to the application.

Regarding the technical description, the information needed are the title and the abstract; the list of "claims" regarding the specific fields and the scope of the protection; the prior art which describes the boundaries of what is in the public domain; we can also find the different kind of references and citations.

For the purpose of this analysis, the references and the citations hold a crucial role. In fact, as for the OECD Patent Manual (2009), citations are those references usually presented in the search report. Those citations can be patents too or non-patent citations. They are used to decide if the invention has the right of patentability and help to define the legitimacy of the claims. They also can be used to indicate the legal boundaries of the invention creating an important link with the claims. Citations are described as patent references when they are citations to a technology protected by a patent. On the other hand, they are defined as non-patent

literature (NPL), when we talk about scientific publications, books, database guide, etc.

It is important to notice also that non-patent references have to be considered with caution since the difference among the patent offices can change the number and type of references. For instance, at the EPO, the references are assigned after the revision of an examiner. As a consequence, usually they do not reflect the science used in a particular patent (Tijssen, 2002).

As for the OECD Patent Manual (2009), citations can also be classified as backward and forward. The backward citations are the patents, and NPL cited in the document analyzed. While the forward citations are the citations received after the publication. Those kinds of data are important to build indicators that will allow not only to study the technology level in that field but also to understand the value of the patent in details.

Moreover, Authors, mentioned that in the development and ownership category could be found information about the list of the inventors, that most of the time are employees of the applicants. The applicants are the ones that have a legal title to the patent, for this reason in most of the cases, applicants are the companies.

To collect data regarding the history, patents represent information regarding the processes, using different kind of dates. Since there exist several dates, there could be problems when a patent needs to be analyzed. So, the most appropriate one

should be chosen. Also, it should be noticed that according to the different offices, they could have a different meaning. Among those dates, there are:

- The publication date, which represents when the information is shared to the public and it usually corresponds to the period after 18 months from the priority date (with an exception for specific applications in US where they publish it when granted).
- The application date, which is the date in which the patent is filed to the office. Usually, applicants decide to first file the patent in the national office (creating a priority date) and then extend it, to other countries' offices, generating a 12-month lag.
- The patent grant number, in which the rights are given to the applicant. According to the offices and authorities, it could take different time. For instance at the EPO it takes five years, while at the USPTO three.
- The priority date, which is the first filing date of the patent, anywhere in the world. For this reason, it is considered to be the one that represents the first priority and the closest date to the invention. In this type of application, a number is given. It is used to identify the priority country and the patent family.
- Other dates are the date of refusal or withdrawal and the date of lapse (OECD Patent Manual, 2009).

3.2 METHODS

In this patent analysis, the “Espacenet” from the European Patent Office (EPO) and “Patentscope” of the World Intellectual Property Organization (WIPO) databases were used. The choice has been made after having analysed papers and methods used in this field, such as the ones developed by Nascimiento (Nascimiento et al., 2020). From the analysis of these papers and articles, the most efficient and more suitable databases have been chosen. Moreover, they are also the most updated for the aim of this analysis.

It is important to notice and keep in mind that we are not going to take into consideration every patent where the mabs are used. This is due to the fact that sometimes this kind of antibodies are used also for the diagnostic of viruses such as the sars-cov-2, not only for therapeutic purposes. Therefore, a research and screening phase regarding the purpose of each patent has been done.

On both databases, several queries with the same combination of key words have been made. In particular in the section dedicated to title, abstract or names, the keywords chosen were:

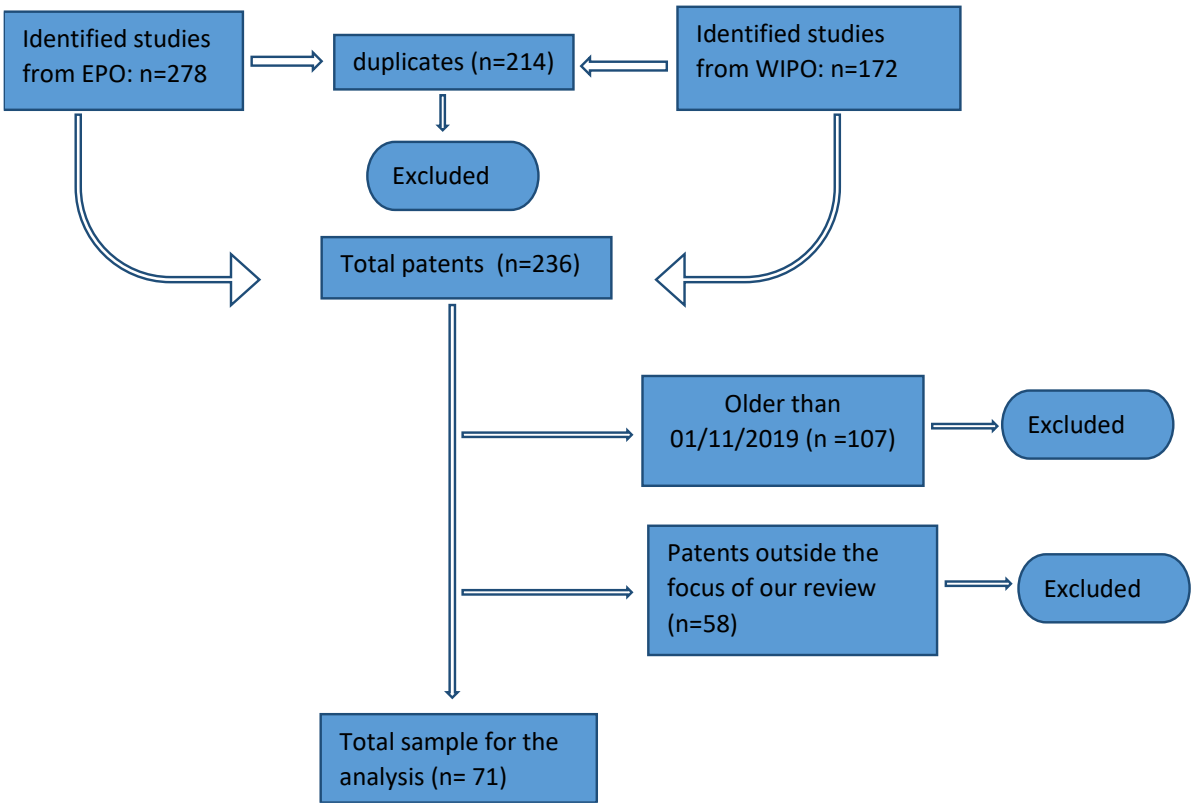
1) “monoclonal” together with “covid19” “Sars-Cov-2” or “2019-nCoV”.
2) “monoclonal” and “coronavirus” with a period of time of 2018-2021.
3) “antigen-binding fragment” and “coronavirus” with a period of time of 2018-2021 together with an IPC “C07K 16/10”.

From the databases a total of 450 patents have been downloaded (EPO= 278 and WIPO=172). Then, 214 patents have been removed since duplicates; 107 documents have been excluded due to the fact that they have a publication date after 01/11/2019. The publication date is the date in which the document is published and starts to be considered part of state of the art. For this reason, to be sure regarding the analysis, a safe date, set well before the WHO declaration of the pandemic situation (12 March 2020), has been chosen.

After this step, there has been a screening phase. Indeed, all those documents that were outside of the focus of our review, have been excluded. This screening phase has taken into consideration first the title presented in the patent. If the title specifically referred to the diagnostic purpose of the antibody, the patent has been excluded. Then, if it hasn't been possible to recognize the aim of the patent from the title, a full reading of the description of the patent has been conducted. Consequently, 58 documents have been excluded since focused on the diagnostic scope of the mAbs, and not on their therapeutic purpose.

Finally, 71 patents were selected for our critical analysis according to the objective of the study. The Figure 6 illustrates the flowchart of the patent search.

Fig 6: Flowchart of patent search and screening



Source: Own elaboration

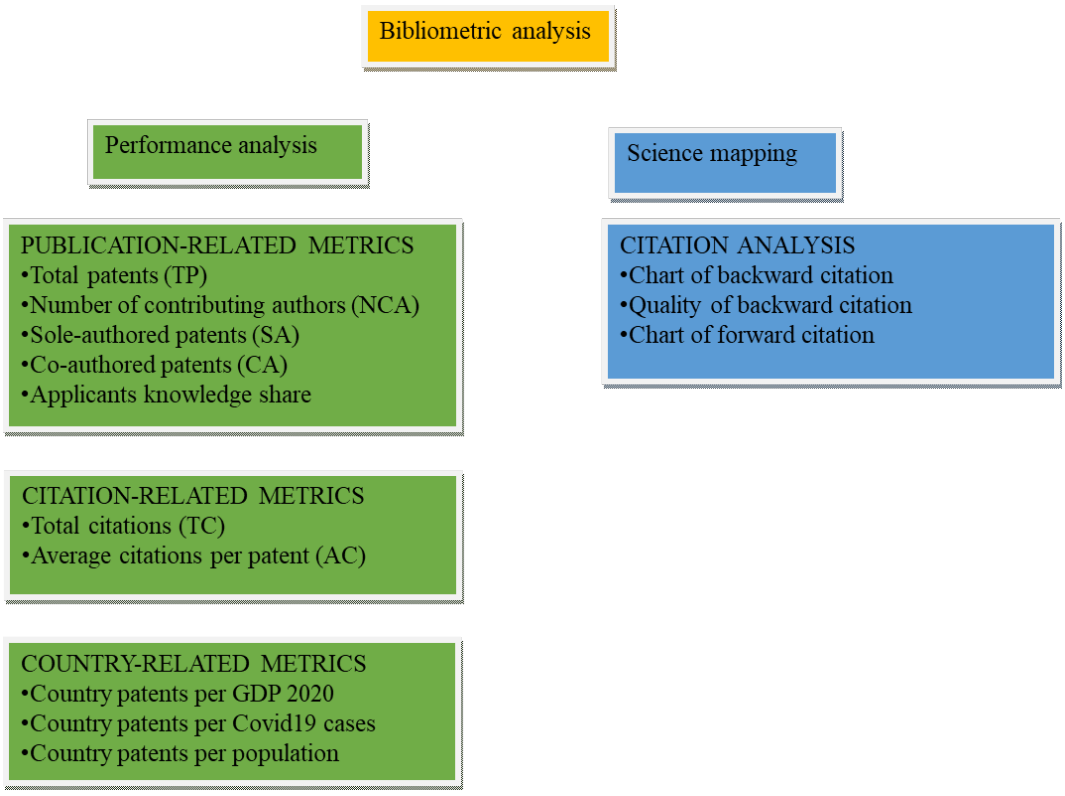
The databases chosen allows to download data regarding the publication code created by the entities when the patent is published, the title, the inventors, the applicants, the publication date and the family number. Once extrapolated, the data have been elaborated on an Excel file keeping into consideration the indicators that are more important in our analysis. Appendix A shows the final list with the 71 patents analysed and with the meaning full information. Also, a patent number that

goes from 1 to 71 that has been associated to each of them, in order to be clearer and more precise recognizing them.

3.2.1 THE CHOSEN INDICATORS

As mentioned before, performance analysis is a method used with a descriptive purpose and it is often utilized to study the performance of the components of the analysis, such as the authors or inventors or the number of the citations done. For the purpose of this study, the most suitable metrics among the performance analysis and science mapping will be taken into consideration. Those metrics can be found on Figure 7.

Figure 7: Bibliometric analysis metrics



Source: Own elaboration based on Donthu et al. (2021)

The performance analysis is then divided into subgroups. First, it is presented the publication-related metrics. In this case, several indicators are going to be taken into consideration:

- The total publications (TP) of the research, that in our case will be the total number of the patents inherent to the analysis.
- The total number of authors that contribute to publications (NCA) that in our case will be the inventors of the technologies patented.

- An analysis of the applicants and a focus if there exist sole-authored patents (SA) or co-authored patents (CA).
- The "applicants knowledge share" (AKS) which is a metric created during the process of this research, takes into account the percentage of contribution of the applicants and highlights the highest presence of knowledge among them.

Among the citation-related metrics, there are going to be chosen metrics such as:

- The number of total citations (TC)
- The average citations per patents (AC) with a specific focus on the division of forward and backward citations.

Moreover, some metrics related to the counting of the country specific patents are going to be calculated. For each country, data and information regarding the GDP 2020, the Covid-19 cases and the population are going to be extrapolated. The metrics are:

- The country patents per GDP (CPGDP). It establishes the amount of patents for each billion dollars of GDP. And is calculated as:

$$CPGDP = \frac{Country\ patents}{GDP}$$

- The country patents per number of Covid-19 cases (CPCOV). It establishes the amount of patents for each million of covid19 cases. And is calculated as:

$$CPCOV = \frac{Country\ patents}{Covid19\ cases}$$

- The country patents per population (CPPOP). It evaluates the patents for each million of population. It is calculated as:

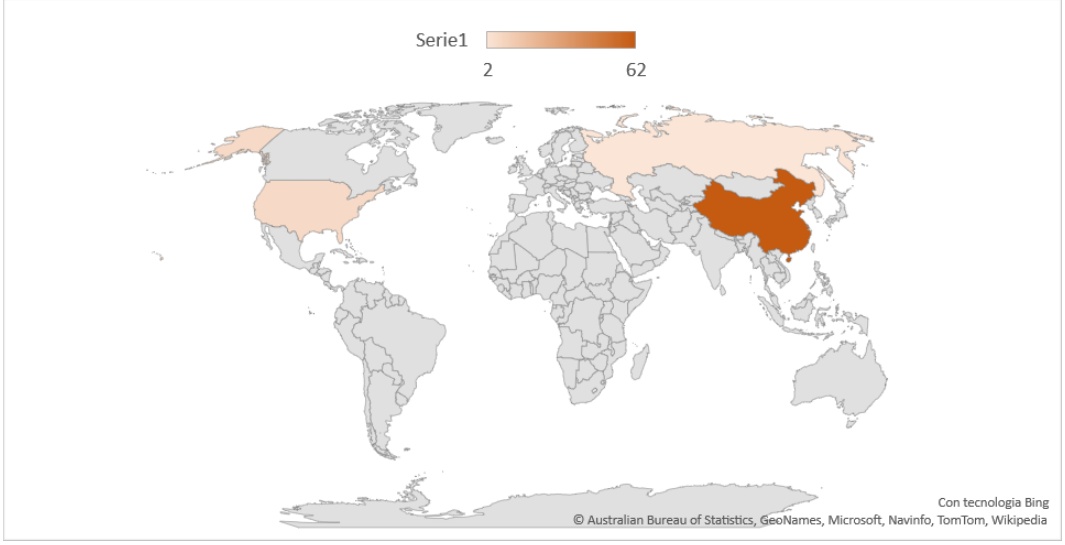
$$CPPOP = \frac{Country\ patents}{population}$$

To conclude, among the science mapping techniques, a citation analysis has been developed. In particular, citations of each patents have been analysed and counted, in order to understand the quantity and the quality of the backward and forward citations. Among the citations, there are different type of references, such as patents citations and non-patent literature. For these citations, some charts have been created to classify the documents that have been cited more (backward citations) and from which patents and to classify the common forward citations of some patents.

3.3 ANALYSIS AND RESULTS

In our review, the total patents taken into analysis in this study are 71 and their publication date report dates that cover the period from 2020 to June 2021 since they cover the specific period of the emergence of SARS-CoV-2. Regarding the patents, the countries with the most filings were China (CN) with 62 patents, the United States (US) with 7 patents and Russia with 2 patents. The distribution is depicted in Figure 8. This analysis has depicted a leading role situation China, which could be first associated with the fact that it is the country in which the pandemic originated.

Figure 8: Patents per country



Source: Own elaboration

Once calculated the total patents per each country, some country-related metrics have been developed. Indeed, data regarding the GDP during 2020 have been

downloaded. Moreover, from the official WHO[20] website, information regarding the number of Covid19 cases declared by the governments and the level of population of each country have been collected and reported in Table 3. As it can be seen, the GDP is expressed in US billion dollars, the Covid-19 cases and population in millions, in order to have more understandable results. Please notice that in particular for Covid-19 cases, those are information declared by each government, as a consequence even if the low number of Chinese cases could seem unrealistic, we are going to take the data as they are stated. As a consequence, the corresponding result could represent an unrealistic situation too. Then, the country related metrics explained in Figure 6 are calculated and the results are reported in Table 4.

Table 3: Country related information

	China	United States of America	Russia
GDP 2020 (in billion US dollars)	14722.84	20934.9	1473.58
Covid-19 cases (in millions)	0.12	35.66	6.49
Population 2020 (in millions)	1443.6	328.2	144.4

Source: Own elaboration. Data collected from WHO and Statista.

[20] https://covid19.who.int/table

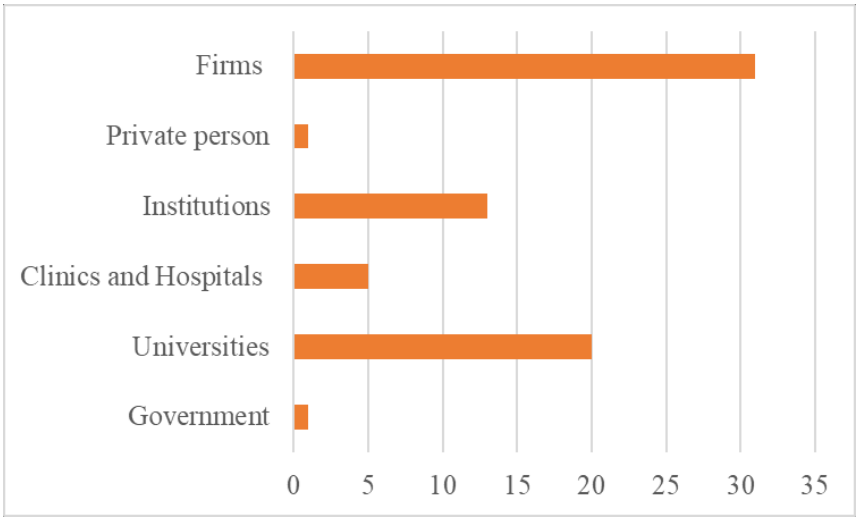
Table 4: Country related results

	China	United States of America	Russia
Country patents/ GDP 2020	0.0042	0.0003	0,0014
Country patents/ Covid-19 cases	508.88	0.20	0.31
Country patents/ Population 2020	0.04	0.02	0.01

Source: Own elaboration

Furthermore, the total number of inventors (NCA) results to be 480, with an average of 6.76 inventor per patents. The number of sole authored (SA) is just 1 while, all the others are co-authored patents (CA). In addition, the total applicants for the 71 patents are 37 and for each patent, they have been analysed and divided into public or private entities. The public ones are 39 while the private 32. Each group is then divided into subgroups. The private one is formed of 1 applicant represented by a private person, while 31 come from firms and entities such as *Regeneron Pharma, Centivax inc., the Whuan Institute of Biological products Co Ltd.*, or the *Jiangsu Jicui Institute of medical immunology Tech CO Ltd*. The public group has been divided into subgroups such as Universities (20 patents), Institutions (13), Clinicals and Hospitals (5) and the government (1). The situation is depicted in Figure 9.

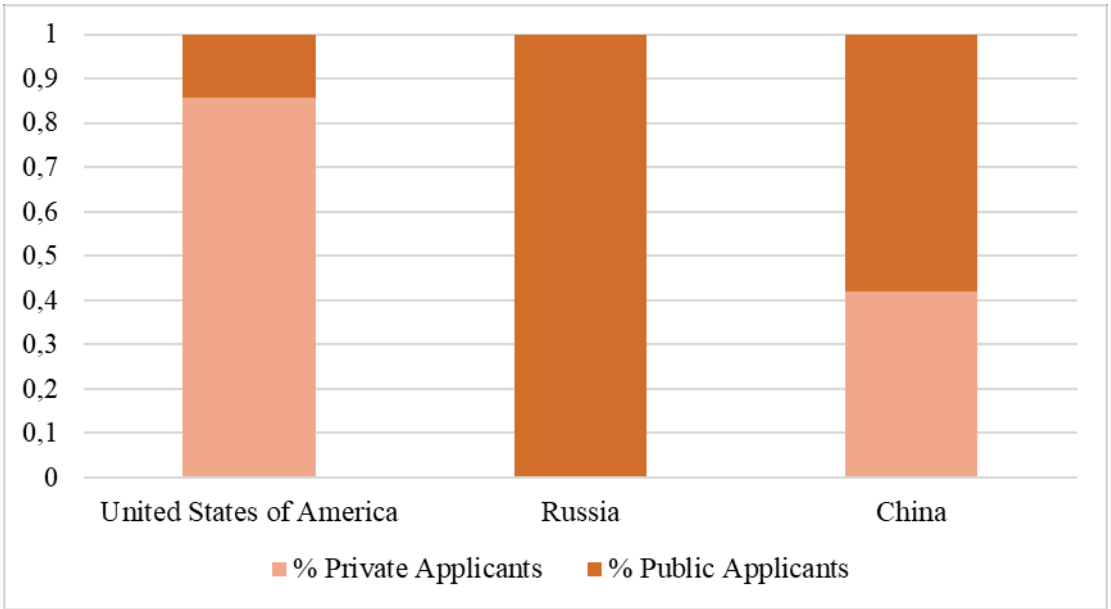
Figure 9: Applicants classification



Source: Own elaboration

Then, the distinction between public and private applicants has been applied to the three countries. As could be imagined, the division reflects the political situation of each country: most of the patents of China and Russia come from applicants in the public sector, while is the contrary for the United States. In particular, Russia has 2 public applicants; China has 26 private applicants and 36 private ones; United States of America count 6 private and 1 public. The percentages are reported in Figure 10

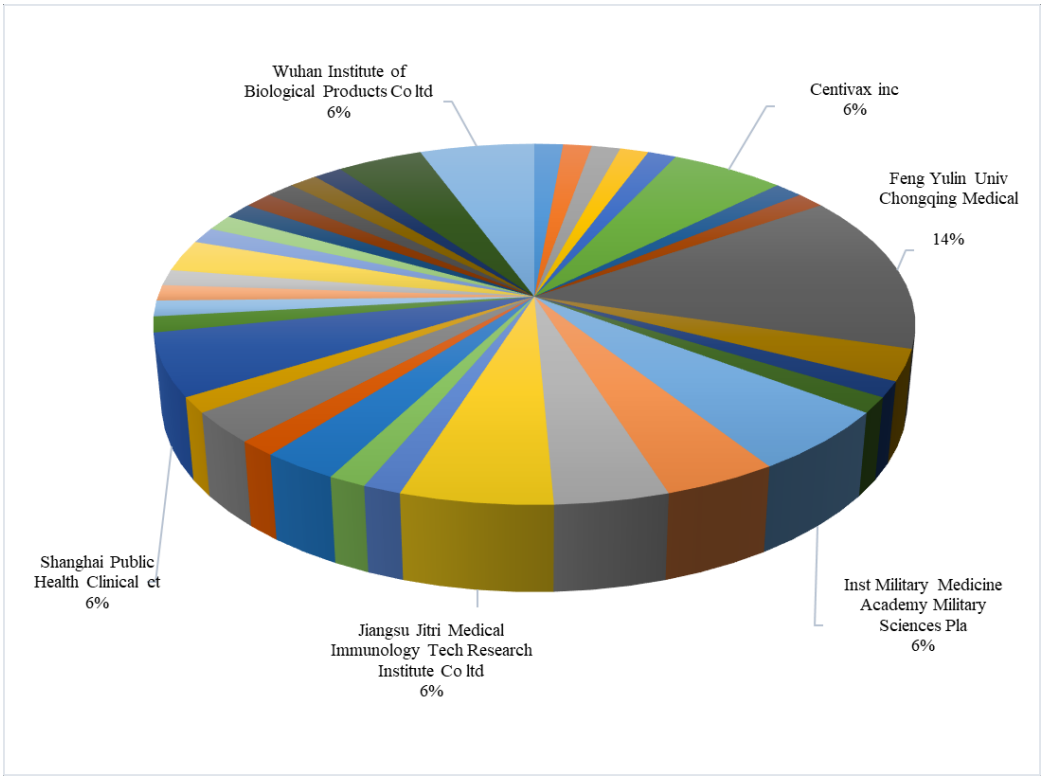
Figure 10: Percentage of public and private applicants per country



Source: Own elaboration

Then, the "applicants knowledge share" has been calculated. This indicator has been created in order to depict the percentage of the contribution to each applicants in this analysis compared to our total patents in the research field of the monoclonal antibodies' therapy for Covid-19. From the results, the applicant with the highest score (10 patents) is the *Chongqing Medical University by Feng Yulin*. The second ranked are the *Wuhan Institute of biological products, the Shanghai public Health Clinical, the Jiangsu Jitri Medical immunology rech. Research Institute, the Institute military medicine Academy military science and Centivax Inc*. All of them with 4 patents each and all of them from China, apart from *Centivax* which is from US. See Figure 11.

Figure 11: Applicants knowledge share



Source: Own elaboration

In addition, to pursue a citation analysis, for each of the 71 patents, the list of backward and forward citations has been downloaded. The total number (TC) in general is 303, of which 257 patents (85% of the total) are backward citations, while 46 (15%) forward. The average citations (AC) per patent is 4.23.

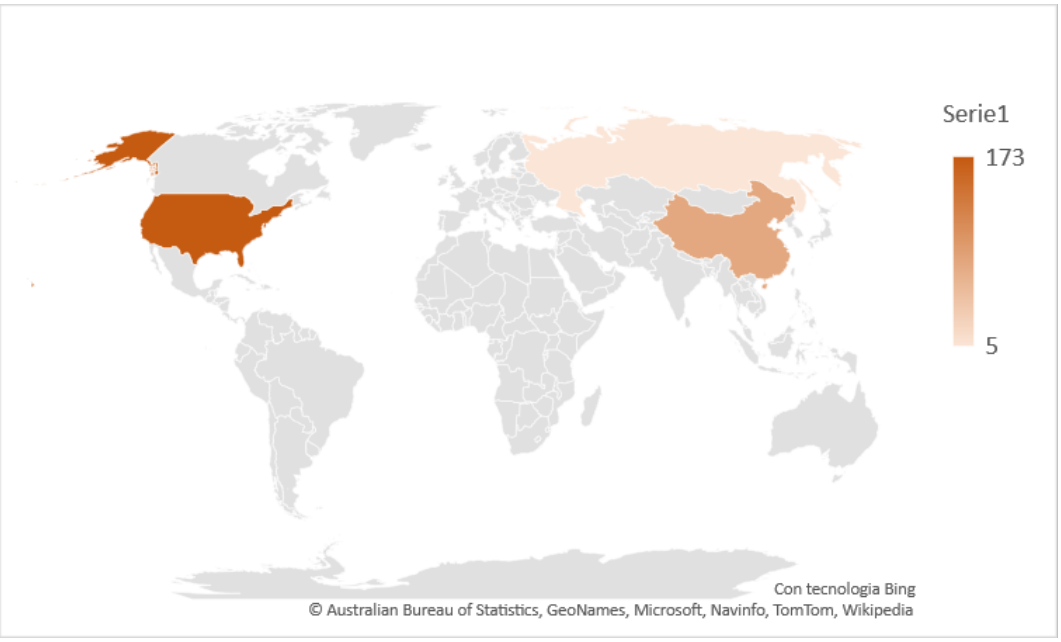
Also in this case, the analysis has been applied to the countries.

- The highest level of citations is reported by the United States with 175 citations, of which 173 backward and only 2 forward.

- Then we have the Chinese citations, 123 citations, of which 79 backward and 44 forward.
- Finally, we have Russia with the 5 citations, all of them backward.

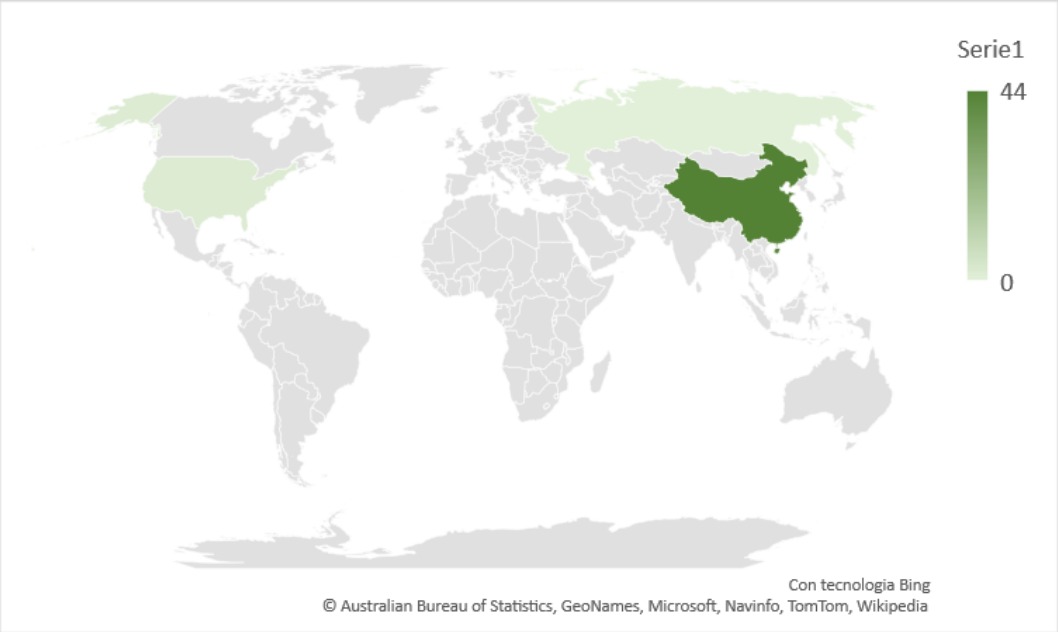
The backward and forward situations are represented in the Figures 12 and 13.

Figure 12: Representation backward citations per countries



Source: Own elaboration

Figure 13: Representation forward citations per countries



Source: Own elaboration

As explained before, the citations can be patent references or non-patent literature. Consequently, to calculate them, information regarding each patent have been studied. Indeed, the title, the inventors/authors of each citation and above all the type of document (patent, scientific paper, article, interview etc.) have been extrapolated from the databases.

In this way, the results have shown that the citations that are patents correspond to 132, while all the other kind of citations (non-patent literature) are 171. These 171 non-patent literature are cited documents (backward citations). In particular, they are not only science articles, but also interviews, videos and twitter references. In

addition, the citations that are repeated in more than one patent have been highlighted and the most significant ones have been reported.

Among the forward citations:

-The patent CN112679605A "Antibody or antigen binding fragment thereof for novel coronavirus nucleocapsid protein and application of antibody or antigen binding fragment thereof" has cited 3 patents, that correspond to our list number: 2, 41, 43.

- The patent CN112225806A "Neutralization activity monoclonal antibody of humanized anti-novel coronavirus (SARS-CoV-2)" has cited 3 patents as well: 7,8 and 9. 8 and 9 come from the same applicant: *Jiangsu Disease Control And Prevention Center Jiangsu Public Health Inst.*

-The patent CN112666350A "Test paper and kit for detecting novel coronavirus" has been cited by patents 2, 11 and 20.

-The patent CN112326962A "Novel coronavirus antigen colloidal gold rapid diagnosis kit and preparation method thereof" has been cited by 13 and 17, both of which applicant is the *Wuhan Inst Of Biological Products Co Ltd*.

-The patent CN111961133A "Monoclonal antibody capable of aiming at SARS-CoV-2 spike protein non RBD (Receptor Binding Domain), and application of monoclonal antibody" has been cited by patents 26 and 36.

Furthermore, if we analyze the backward citations, the documents that we can find are not only patents, but also non-patent literature. Indeed, among all the backward

citations, the ones that have been cited more and are more significant have been highlighted. The patents cited more than once are:

-Patents 8 and 9, both from the *Jiangsu Disease Control And Prevention Center Jiangsu Public Health Inst* have cited patent CN111024954A "Colloidal gold immunochromatography device for combined detection of COVID-19 antigen and antibody and use method thereof".

- Patents 45 and 50 have cited patent CN111620945A "Monoclonal antibody for resisting novel coronavirus or derivative thereof".

-Patents 50 and 55 have cited patent CN111592594A "Anti-novel coronavirus monoclonal antibody and application thereof".

For what concerns the non-patent backward citations:

-There are two patents, 20 and 69 that cite the same scientific article: "A human monoclonal antibody blocking SARS-CoV-2 infection".

-Moreover, the patents 63, 64, 65 and 66 (that show the same inventors and applicant: *Centivax Inc*) have all the same and identical 30 NPL references. Among those references, some of them are videos and interview from non scientific papers. Moreover, some of them are also social media posts, such as twitters. As a consequence, the inappropriate ones have been excluded and the most significant science articles have been highlighted:

- Tian et al. "Emerging Microbes and Infections" 2020.

- Hwang et al. “Structural basis of neutralization by a human anti-severe acute respiratory syndrome spike protein antibody”. R. J Biol Chem. Nov. 10, 2006.
- MacCallum et al. J. Mol. Biol. (1996)
- Rudikoff et al., Proc Natl Acad Sci USA (1982).
- Walls et al. “Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion” (2019).
- Cohen. “The race is on for antibodies that stop the new coronavirus”. Science (2020).
- Prabakaran et al. “Structure of severe acute respiratory syndrome coronavirus receptor-binding domain complexed with neutralizing antibody”. J Biol Chem. (2006).

The results are reported in Table 5 and Table 6, to represent the two charts with the times that each reference is cited and in which patent (in case of backward citations) and to represent which patents, among the 71 that we analyzed, are cited together (in case of forward citations).

Table 5: Chart of forward citations

FORWARD CITATIONS	TIMES	PATENTS CITED
patent CN112679605A	3	2; 41; 43
patent CN112225806A	3	7; 8; 9
patent CN112666350A	3	2; 11; 20
patent CN112326962A	2	13; 17
patent CN111961133A	2	26;36

Source: Own elaboration

Table 6: Chart of backward citations

BACKWARD CITATIONS	TIMES	IN WHICH PATENTS
Tian et al. Emerging Microbes and Infections, 2020.	4	63;64;65;66
Hwang et al. Structural basis of neutralization by a human anti-severe acute respiratory syndrome spike protein antibody, 80R. J Biol Chem. Nov. 10, 2006.	4	63;64;65;66
MacCallum et al. J. Mol. Biol.1996.	4	63;64;65;66
Rudikoff et al., Proc Natl Acad Sci USA 1982.	4	63;64;65;66
Walls et al. Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion. Cell. 2019.	4	63;64;65;66
Cohen. The race is on for antibodies that stop the new coronavirus. Science, 2020.	4	63;64;65;66
Prabakaran et al. Structure of severe acute respiratory syndrome coronavirus receptor-binding domain complexed with neutralizing antibody. J Biol Chem.2006.	4	63;64;65;66
patent CN111024954A	2	8; 9
patent CN111620945A	2	45; 50
patent CN111592594A	2	50; 55
Chunyan Wang, A human monoclonal antibody blocking SARS-CoV-2 infection. Nature Communications.	2	20; 69

Source: Own elaboration.

To sum up, the indicators and the results have been collected in Table 7 and some final considerations will follow in the conclusions.

Table 7: Final results

INDICATORS	RESULTS
TOTAL PATENTS (TP)	**71**
• Chinese patents	62
• US patents	7
• Russian patents	2
NUMBER OF CONTRIBUTING AUTHORS (NCA)	**480**
SOLE-AUTHORED PATENTS (SA)	**1**
CO-AUTHORED PATENTS (CA)	**70**
TOTAL APPLICANTS	**37**
PATENTS WITH PRIVATE APPLICANTS	**32**
• Private person	1
• Firm/entities	31
PATENTS WITH PUBLIC APPLICANTS	**39**
• Universities	20
• Institutions	13
• Clinics/Hospitals	5
• Government	1
% OF PUBLIC AND PRIVATE APPLICANTS	
• Chinese applicants	42% private; 58% public
• US applicants	86% private; 14% public
• Russian applicants	0% private; 100% public
COUNTRY PATENTS PER GDP (CPGDP)	
• China	0.0042
• United States of America	0.0003
• Russia	0.0014
COUNTRY PATENTS PER COVID19 CASES (CPCOV)	508.88
• China	0.20
• United States of America	0.31
• Russia	
COUNTRY PATENTS PER POPULATION (CPPOP)	0.04
• China	0.02
• United States of America	0.01
• Russia	
TOTAL CITATIONS (TC)	**303**
AVERAGE CITATIONS PER PATENT (AC)	**4.23**
TOTAL BACKWARD CITATIONS	**257**
• China	79
• United States of America	173
• Russia	5
TOTAL FORWARD CITATIONS	**46**
• China	44
• United States of America	2
• Russia	0
PATENT CITATIONS	**132**
NON-PATENT CITATIONS	**171**

Source: Own elaboration

CONCLUSIONS

The aim of this study is to provide a detail scenario of the actual situation of the monoclonal antibodies therapies for the Covid19 through the analysis of the patents and the related regulation.

This dissertation starts with the biological and scientific introduction of the main topics of the work: the monoclonal antibodies, the Sars-CoV-2 and their use in the treatment of the Covid-19.

Understanding those subjects together with their structures and functions lays the foundations for the comprehension of the following chapters. Monoclonal antibodies are glycoproteins that during the years have been utilized to cure and treat other diseases.

Nowadays, we have been obliged from the pandemic situation to adapt all the possible weapons to contrast this virus, and the mAbs are one of them. Those specific antibodies can do that, exploiting the connection to a particular protein, called Spike protein, and being able to block the infection.

Then, the second chapter goes on with the representation of a process, that starts with the recognition of the importance of the intellectual property rights and ends up with the introduction of drugs in the market. This chapter at first presents the general aspects of the patents - for instance their advantages and disadvantages as an instrument of protection or indicator of knowledge, both from the European and American point of view.

Then, once the general characteristics are understood, for the purpose of this analysis, a focus on the pharmaceutical sector was needed. Each sector in the market has its own characteristics, but the pharmaceutical one can be considered very peculiar. It has the possibility to use different types of patents and it is also subjected to a specific regulation from the health authorities of each country. For this reason, the responsible authorities have been introduced together with their standards. However, among the pharmaceutical patenting characteristics, the interesting aspects regarding the patenting of the monoclonal antibodies have been highlighted. To understand the patentability cases of the mAbs depicted by Germinario et al. (2018), the biological and structural introductions of the mAbs and of Sars-CoV-2 done in chapter 1 resulted to be fundamental. Patenting the monoclonal antibodies represents a challenge that depends on their ability to bond with an epitope on the surface of the antigen.

Once property rights have been established, the pharmaceutical companies have to organize the introduction of drugs into the market. As before, each country follows specific jurisdiction and principles of their authorities, for this reason the European and United States cases are described separately also this time.

All the information and knowledge regarding patents collected in the second chapter then is used to understand the concepts, and interpret the results of the empirical analysis done in chapter 3. Indeed, as mentioned before patents are not only protection rights instruments, but also innovative and knowledge

representations. However, to be able to use that information, a patent analysis should be performed through the use of bibliometric indicators. For this reason, this field of research and its history were presented together with the possible applications to the patent sector. Particularly, the indicators chosen in this review have been extrapolated and derived from the concepts of “performance analysis” and “science mapping” described in Donthu et al. (2021).

In order to pursue this analysis, a dataset of 71 patents has been established. The data have been collected from two databases: “Espacenet” of EPO and “Patentscope” of WIPO through a combination of specific keywords and after having submitted all the data to a screening phase.

The empirical analysis results have depicted a renovation in the state of the art for the monoclonal antibodies therapy for Covid-19 together with an outstanding presence of one country over the others. Indeed, three countries were considered from the results: China, United States and Russia with an extravagant leading role of China as major inventor country. The second country is the United States while the third one is Russia. In addition, most of Chinese patents have been developed prior in time, from the very first months of the beginning of the pandemic, compared to the American and Russian ones, which have been patented later on, from the 2021. Then, the analysis has also taken into consideration, for each patent, the inventors, the applicants and has depicted the results in graphical tools presented in chapter 3.

The patent scenario, as already mentioned, has described a leading role of China, which could be first explained considering that the Sars-Cov-2 virus, as well as other virus, originated in that country. Indeed, in China, meat and live animal markets are common and in rural areas, people are used to encounter wild animals (Sisk et al., 2015). So, the closeness to the virus together with the Sars-CoV-2 neglection from the government point of view and the high spreading power of the virus, have led to an uneven patent situation among countries.

However, this closeness to the epicenter of the pandemic explains in part the promptness of this country in the patent application but leaves some shadows regarding this topic. Indeed, interesting aspects are also related to the fact most of Chinese patent applicants of monoclonal antibodies are public institutions, probably sustained by the government. Consequently, it should be asked why the Chinese government is so interested in the development of this cure, even more so if the government itself has declared to the WHO the occurrence of very low numbers of Covid-19 cases, compared to the other countries (Table 3).

Furthermore, the division among public and private applicants among these countries reflect their political situation, Indeed, most of the United States patents are reported to be from privates, while most of the patents from China and Russia are from public entities.

The differences among the countries follow with the citations, backward and forward and their quality. United States show a completely different way of citating

in their patents. The situation points out that US patents are made up of a high quantity of backward citations and a very low number of forward ones. Moreover, most of the American backward citations come from non-patent literature. Indeed, as mentioned in the previous chapter, in this analysis non-patent citations consider not only scientific articles and papers, but also unofficial interviews and social media posts, such as twitters. Therefore, even if all the three countries have the tendency to have more backward citations than forward ones, the American choice of privileging informal references lowers a lot the quality level of the citations compared to Chinese and Russian ones.

On the other hand, most of Chinese citations are patent citations, specifically they are almost Chinese patents as well. However, there exist few citations to patents that come from US, Russia and Japan. In case of non-patent literature, they always take into analysis official scientific papers.

From what concern Russia, establishing a general trend results to be quite difficult. However, what could be noticed is that the citations from the Russian patents are only five and all of them are backward citations. Among those five citations, two are scientific papers, one is a patent citation from Russia while the other two are patent citations from China.

In conclusion, this review shows some strengths and some limitations. Among the strengths, it should be stated that it highlights and emphasize the importance of patent analysis and bibliometric indicators as a useful source to collect information

and knowledge regarding a sector. Indeed, it could happen that companies and inventors prefer to hide their innovations from the scientific community, not publishing scientific articles.

On the other hand, this study also presents some limitations. First, the Covid-19 topic could be considered a young sector and a fast-changing field of study. Furthermore, it could happen that some companies decide not to patent immediately their antibodies or there could be a bias in the inclusion of the patent, due to the 18-month confidentiality period that patent offices grant to inventors.

In order to overcome this bias, the study has been carried out on relevant databases and with the use of complete key words in a careful selection process.

To conclude, as already mentioned, patents can provide a general overview and description of the knowledge in different sectors, that can be transformed in benefits. Those benefits are not only in economic terms, but also from a social and health point of view, due to the importance of making progresses in the war against Covid-19. Therefore, those benefits, particularly the economic ones, could be the explanation regarding the disproportionate Chinese share of patents in this sector. Moreover, the Chinese monoclonal antibodies patent scenario compared to the pharmaceutical one could lay the foundations for the future research agenda.

In conclusion, the relevance of mAbs in terms of therapies for the cure of the Sars-CoV-2 virus should reinforce and incite researchers and professionals to perform

patent analyses in order to define the level of knowledge and set the groundwork for new discoveries.

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APPENDIX

Appendix A: Final list of mAbs patents for sars-cov-2 therapy

N patent	Publication number	Title	Inventors	Applicants
1	CN111053909A	Application of 2019-nCoV3CL hydrolase inhibitor and IL-6 monoclonal antibody in preparation of treatment novel coronavirus pneumonia drug	Jiang Zhenglin Li Xia Luo Qianqian Sun Yechao Wang Guohua Xu Lihua Ye Lisha Zhou Jiamin	Univ Nantong
2	CN111153991A	Human SARS-CoV-2 monoclonal antibody and preparation method and application thereof	Dong Bing Qin Lina Wang Dongdong Wu Ju Wu Xiaole Zhang Fengying Zhao Fengqiang	Beijing Biosynthesis Biotechnology Co ltd
3	CN111303280A	High-neutralizing-activity anti-SARS-CoV-2 fully-humanized monoclonal antibody and application thereof	Chen Wei Chen Yi Chi Xiangyang Dong Yunzhu Fan Pengfei Fang Ting Fu Ling Hao Meng Hou Lihua Li Jianmin Liu Shuling Song Xiaohong Xu Junjie Yu Changming Zhang Guanying Zhang Jinlong Zhang Jun	Inst military medicine academy military sciences pla
4	CN111454354A CN111454354B	2019-nCoV resistant antibody, preparation and preparation method and application of preparation	Gao Yuwei Liu Mingyuan Liu Xiaolei Sun Yansong	Univ Jilin
5	CN111471105A	Preparation and application of silver therapy neutralizing antibody for treating 2019-nCoV	Huang Yong Zhao Yongxiang Zhong Liping	Univ guangxi medical
6	WO2020167919A1	COMPOSITIONS AND METHODS FOR USING	Kyratsous Christos Lin Chia-yang	Regeneron pharma [us]

		BISPECIFIC ANTIBODIES TO BIND COMPLEMENT AND A TARGET ANTIGEN	Murphy Andrew j Prasad Brinda Stahl Neil	
7	CN111592594A	Anti-novel coronavirus monoclonal antibody and application thereof	Cao Yunlong Sun Wenjie Xie Xiaoliang	Univ Beijing
8	CN111620946A CN111620946B	Isolated novel coronavirus monoclonal antibody or antigen binding part thereof	Guo Xiling Li Jingxin Pan Hongxing Wang Xiangxi Zhang Li Zhu Fengcai	Jiangsu disease control and prevention center jiangsu public health inst
9	CN111620945A CN111620945B	Monoclonal antibody for resisting novel coronavirus or derivative thereof	Chen Yin Gao Xingsu Guo Xiling Li Jingxin Wang Xiangxi Zhang Li Zheng Binyang Zhu Fengcai	Jiangsu disease control and prevention center jiangsu public health inst
10	CN111690059A	Anti-SARS-CoV-2 monoclonal antibody 1D7	Chen Ying Deng Xiaojie Du Jianhui Duan Kai Gui Fang Jing Zhaofei Li Xinguo Liu Jianbang Pan Yongbing Song Gang Wang Jiong Wu Xiaoli Yang Xiaoming Yang Yimin Zhan Shanshan Zhang Nan Zhang Zhi	Wuhan inst of biological products co ltd
11	CN111690058A CN111690058B	Antibodies with neutralizing activity against coronavirus and application thereof	Han Xiaogang Hu Yuhao Kong Chao Lang Guojun Shao Junbin Sun Xinglu Tan Yongcong Tian Mei Wu Qi Yan Run Yan Xintian Yao Fujia	Sanyou bio inc shanghai zj bio tech co ltd

			Yao Hangping Zhang Wenhai Zhou Yunhua	
12	CN111704666A	Paired monoclonal antibodies of novel coronavirus (SARS-CoV-2) N protein and application of paired monoclonal antibodies	Chen Shiping Dong Hongyan Feng Changfang Jiang Yi Wang Baojun	Beijing kewei clinical diagnostic reagent inc
13	CN111718411A	Anti-SARS-CoV-2 monoclonal antibody 1F2 and preparation method thereof	Chen Ying Deng Xiaojie Du Jianhui Duan Kai Gui Fang Jing Zhaofei Li Xinguo Liu Jianbang Pan Yongbing Song Gang Wang Jiong Wu Xiaoli Yang Xiaoming Yang Yimin Zhan Shanshan Zhang Nan Zhang Zhi	Wuhan inst of biological products co ltd
14	CN111733141A	Hybridoma cell capable of secreting an anti-novel coronavirus N protein monoclonal antibody, onoclonal antibody and application	Cen Yu Ma Lan Wu Feng	Tsinghua shenzhen int graduate school

15	CN111732655A	RBD-targeted high-neutralizing-activity anti-SARS-CoV-2 fully humanized monoclonal antibody and application	Chen Wei Chen Yi Chi Xiangyang Dong Yunzhu Fan Pengfei Fang Ting Fu Ling Hao Meng Hou Lihua Li Jianmin Liu Shuling Lyu Peng Song Xiaohong Xu Junjie Yu Changming Yu Ting Zhang Guanying Zhang Jinlong Zhang Jun	Inst military medicine academy military sciences pla
16	CN111732664A CN111732664B	Novel coronavirus recombinant protein, rabbit-human chimeric antibody and preparation method and application thereof	Lu Shuai Sun Yutian Yu Zaijiang Yuan Zhibo Zhao Rongmao Zhu Lin	Beijing jinzhizhun tech co ltd
17	CN111732654A CN111732654B	Anti-SARS-CoV-2 monoclonal antibody 1E10	Chen Ying Deng Xiaojie Du Jianhui Duan Kai Gui Fang Jing Zhaofei Li Xinguo Liu Jianbang Pan Yongbing Song Gang Wang Jiong Wu Xiaoli Yang Xiaoming Yang Yimin Zhan Shanshan Zhang Nan Zhang Zhi	Wuhan inst of biological products co ltd
18	CN111748032A CN111748032B	Antibody against novel coronaviruses and immunoassays using same	Cui Lunbiao Gao Xingsu Guo Xiling Meng Fanyue Wei Mingwei Zhang Li	Jiangsu provincial center for disease control and prevention public health res institute of jiangsu

			Zheng Binyang Zhu Fengcai	
19	CN111778218A	Phage display antibody library and monoclonal antibodies aiming at novel coronavirus SARS-CoV-2 and obtained by panning based on same	Dong Hang Dong Jinhua Shan Xijun	Shandong kuanhezheng biotechnology medicine co ltd
20	CN111793129A	Antibody for specifically binding coronavirus, and antigen binding fragment of antibody	Huang Jinghe Liu Mei Wu Fan	Shanghai public health clinical ct
21	US10822379B1	Molecules that bind to SARS-CoV-2	Chen Chuan Dimitrov Dimiter Stanchev Jelev Dontcho V Li Wei Mellors John W Sun Zehua	Univ of pittsburgh—of the commonwealth system of higher education [us]
22	CN111909261A	New coronavirus RBD specific monoclonal antibody and application	Gao Fengxia Han Xiaojian Hu Chao Jin Aishun Li Luo Shen Meiying Wang Yingming	Feng yulin univ chongqing medical
23	CN111909262A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Jin Aishun Li Tingting Long Yingyi Luo Feiyang Song Shuyi Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
24	CN111909260A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Huang Jingjing Jin Aishun Li Shenglong Li Tingting Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
25	CN111909263A	New coronavirus RBD specificity monoclonal antibody and application	Han Xiaojian Hu Chao Jin Aishun Li Shenglong Li Tingting Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical

26	CN111925440A	Novel coronavirus RBD specific monoclonal antibody and application	Chen Qian Hao Yanan Hu Chao Jin Aishun Mu Song Wang Yingming Wu Ruixin	Feng yulin univ chongqing medical
27	CN111925444A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Jin Aishun Li Shenglong Li Tingting Long Shunhua Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
28	CN111925443A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Jin Aishun Li Shenglong Li Tingting Shen Meiying Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
29	CN111925441A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Huang Jingjing Jin Aishun Li Tingting Shen Meiying	Feng yulin univ chongqing medical
30	CN111925442A	New coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Jin Aishun Li Shenglong Li Tingting Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
31	CN111944026A	Linear epitope of novel coronavirus RBD specific monoclonal antibody and application	Han Xiaojian Hu Chao Jin Aishun Li Shenglong Li Tingting Shen Meiying Wang Jianwei Wang Yingming	Feng yulin univ chongqing medical
32	CN111978398A	Antibody to coronaviruses SARS-CoV-2 and medical	Chen Ling Li Song	Jiangsu jitri medical immunology tech research institute co ltd

		application of antibody to coronaviruses SARS-CoV-2	Niu Xuefeng Yu Fengjia	
33	CN111978397A	Antibody specifically bound to SARS-COV-2 S protein and application of antibody	Chen Ling Niu Xuefeng Wang Chunlin Wang Yang	Jiangsu jitri medical immunology tech research institute co ltd
34	CN111978396A	Antibody specifically binding to SARS-COV-2 NP protein and application thereof	Chen Ling Niu Xuefeng Wang Chunlin Wang Yang	Jiangsu jitri medical immunology tech research institute co ltd
35	CN111978399A	Antibody specifically binding to SARS-COV-2 antigen protein, and use of antibody	Chen Ling Li Song Niu Xuefeng Yu Fengjia	Jiangsu jitri medical immunology tech research institute co ltd
36	CN111995672A	Coronavirus SARS-COV-2 S protein specific antibody and application thereof	Chen Ling Niu Xuefeng Wang Chunlin Wang Yang	Jiangsu jicui medical immunology tech research institute co ltd
37	CN112010963A	SARS-COV-2 antibody and use thereof	Chen Ling Li Song Niu Xuefeng Yu Fengjia	Jiangsu jicui institute of medical immunology tech co ltd
38	CN112010962A	Antibody for detecting COVID-19 and medical application of antibody	Chen Ling Li Song Niu Xuefeng Yu Fengjia	Jiangsu jicui institute of medical immunology tech co ltd
39	CN112010965A CN112010965B	Monoclonal antibody for new coronavirus SARS-CoV-2 spinous process protein RBD region and application of monoclonal antibody	Chen Limei Dong Jinhua Li Haimei	Univ weifang medical
40	CN112062838A CN112062838B	Neutralizing single-domain antibody with function of resisting novel coronavirus SARS-Cov-2 and application of neutralizing single-domain antibody	Ao Lei Gao Wei Liu Xiaoyu Ma Sujuan Ye Wei	Univ nanjing medical
41	CN112079920A	Monoclonal antibody for detecting SARS-CoV-2 virus nucleocapsid protein (N protein) and application thereof	Jin Lizhu Kong Shuangquan Ma Xiaofei Wu Lei Yin Changcheng Zhang Lifan	Beijing protein innovation co ltd
42	CN112076316A	Double-antibody composition and application to preparation	Chen Wei Chen Yi Chi Xiangyang	Inst military medicine academy military sciences pla

		of COVID-19 (Coronavirus Disease 2019) treatment drugs	Dong Yunzhu Fan Pengfei Fang Ting Fu Ling Hao Meng Hou Lihua Li Jianmin Liu Shuling Lyu Peng Song Xiaohong Xu Junjie Yu Changming Yu Ting Zhang Guanying Zhang Jinlong Zhang Jun	
43	CN112111007A	Preparation method of novel coronavirus nucleocapsid protein monoclonal antibody	Miao Lianjun Yong Jingui Zhang Lei Zhang Zhipeng	General biosystems anhui co ltd
44	CN112125973A	Specific antibody of coronavirus, or antigen-binding fragment of specific antibody	Huang Jinghe Liu Mei Wu Fan	Shanghai public health clinical ct
45	CN112159469A	Antibodies of coronavirus or antigen binding fragments of antibodies	Huang Jinghe Liu Mei Wu Fan	Shanghai public health clinical ct
46	CN112175071A	Method for preparing monoclonal antibody of spike protein of novel coronavirus	Miao Lianjun Yong Jingui Zhang Lei	General biol systems anhui co ltd
47	CN112175073A	Neutralizing antibody of coronavirus or antigen-binding fragment thereof	Huang Jinghe Liu Mei Wu Fan	Shanghai public health clinical ct
48	CN112194711A	B cell linear epitope of novel coronavirus S protein, antibody, identification method and application	Feng Tiejian He Jianfan Hu Qinghua Wang Chuan Wang Xiaohui Yang Zhengrong Zhang Yunwen	Shenzhen center for disease control and prevention shenzhen health inspection center shenzhen inst o
49	CN112225797A	Monoclonal antibody of anti-SARS-CoV-2 nucleocapsid protein and application	Ding Haojie Ding Jianzu Gao Meng Kong Qingming Lu Shaohong Xie Chengzuo Yuan Yajie Zhuo Xunhui	Hangzhou medical college

50	CN112225806A CN112225806B	Neutralization activity monoclonal antibody of humanized anti-novel coronavirus (SARS-CoV-2)	Li Yafeng	Li yafeng
51	CN112300274A	Humanized antibody of novel coronavirus specific antigen peptide, preparation method and application	Duan Jing Gao Meiling Li Lili Wan Dingyi Wang Yanan Yang Heng	Suzhou func bio tech co ltd suzhou inst of systems medicine
52	CN112409488A	Monoclonal antibody for various coronaviruses and application	Chen Ganjun Chen Yili Chen Yuning Wang Chunhe Wang Guifeng Wang Qi	Dartsbio pharmaceuticals ltd shanghai inst materia medica cas
53	RU2744274C1	MONOCLONAL ANTIBODY TO RDB FRAGMENT IN COMPOSITION OF SARS-COV-2 S PROTEIN	Antipova Nadezhda Viktorovna Pavliukov Marat Samvelovich Shakhparonov Mikhail Ivanovich	Federalnoe gosudarstvennoe biudzhetnoe uchrezhdenie nauki inst bioorganicheskoi khimii im akademikov
54	WO2021045836A1	ANTI-SARS-COV-2-SPIKE GLYCOPROTEIN ANTIBODIES AND ANTIGEN-BINDING FRAGMENTS	Babb Robert Baum Alina Chen Gang Gerson Cindy Hansen Johanna Huang Tammy Kyratsous Christos Lee Wen-Yi Malbec Marine Murphy Andrew Olson William Stahl Neil Yancopoulos George	Regeneron pharma
55	CN112500481A	Humanized neutralizing active monoclonal antibody against novel coronavirus	Han Chongyang Jin Minlu Li Aizhong Li Rongshan Li Yafeng Liu Xingwei	Shanxi provincial peoples hospital
56	CN112521496A	Monoclonal antibody specifically binding SARS-CoV-2 Spike RBD and application thereof	Dong Ke Gao Zhaowei Liu Chong Wang Xi Zhang Huizhong	Air force medical univ of pla

57	CN112521494A CN112521494B	Monoclonal antibody 2B11 for resisting SARS-CoV-2	Chen Ying Deng Xiaojie Du Jianhui Duan Kai Gui Fang Jing Zhaofei Li Xinguo Liu Jianbang Pan Yongbing Song Gang Wang Jiong Wu Xiaoli Yang Xiaoming Yang Yimin Zhan Shanshan Zhang Nan Zhang Zhi	Wuhan inst of biological products co ltd
58	CN112538111A	Novel coronavirus single-chain antibody, quality control product and preparation method	He Yuxi Hu Kunhui Jiang Zhangtao Li Yirong Lin Jun Lin Xiaotao Pan Yunbao Qian Chungen Wang Gang Wei Daoshun Xing Zhihao	Shenzhen yhlo biotech co ltd
59	CN112552399A	Anti-SARS-COV-2 neutralizing antibody	Li Yuannian Wang Wenyi	Hengyi biomedical tech shanghai co ltd
60	CN112574299A	Humanized antibody of novel coronavirus specific antigen peptide, preparation method and application thereof	Duan Jing Gao Meiling Li Lili Wan Dingyi Wang Yanan Yang Heng	Suzhou func bio tech co ltd suzhou inst of systems medicine
61	CN112574300A	Anti-SAR-COV-2 fully humanized monoclonal antibody as well as preparation method and application thereof	Li Junxin Wan Xiaochun	Shenzhen inst adv tech
62	CN112625125A	Monoclonal antibody for neutralizing novel coronavirus infection	Deng Yongqiang Jiang Tao Kang Xiaoping Li Jing Li Yuchang Qin Chengfeng Wu Xiaoyan	Inst military medicine academy military sciences pla

			Zhang Sen Zhu Qingyu	
63	US11021531B1	Anti-SARS-Cov-2 antibodies derived from 2GHW	Bürckert Jean-Philippe Daraeikia Shahrad Glanville Jacob Liao-Chan Sindy Andrea Wang I-Chieh Youssef Sawsan	Centivax inc
64	US11028167B1	Anti-SARS-Cov-2 antibodies derived from 3bgf	Bürckert Jean-Philippe Daraeikia Shahrad Glanville Jacob Liao-Chan Sindy Andrea Wang I-Chieh Youssef Sawsan	Centivax inc
65	US11028150B1	Anti-SARS-CoV-2 antibodies derived from 2DD8	Bürckert Jean-Philippe Daraeikia Shahrad Glanville Jacob Liao-Chan Sindy Andrea Wang I-Chieh Youssef Sawsan	Centivax inc
66	US11053304B1	Anti-SARS-Cov-2 antibodies derived from 6nb6	Bürckert Jean-Philippe Daraeikia Shahrad Glanville Jacob Liao-Chan Sindy Andrea Wang I-Chieh Youssef Sawsan	Centivax inc
67	CN111423508A	Isolated SARS-CoV-2 protein binding molecule against virus infection	Guo Xiling Jiao Yongjun Zeng Xiaoyan Zhang Wenshuai Zhu Baoli Zhu Fengcai	Jiangsu disease control and prevention center jiangsu public health inst
68	CN112625136A	Bispecific antibody having neutralizing activity against coronavirus and application of bispecific antibody	Hu Yuhao Kong Chao Lang Guojun Liu Chanjuan Shao Junbin Tan Yongcong Yan Run Yan Xintian	Sanyou biopharmaceuticals shanghai co ltd shanghai zj bio tech co ltd

69	CN111961133	Monoclonal antibody capable of aiming at SARS-CoV-2 spike protein non RBD (Receptor Binding Domain), and application of monoclonal antibody	Dong Jinhua Chen Limei Li Haimei	Weifang medical university
70	CN111995676	Monoclonal antibody capable of aiming at corona virus disease 2019 virus spike protein non-RBD (Receptor-Binding Domain), and application of monoclonal antibody	Dong Jinhua Chen Limei Li Haimei	Weifang medical university
71	RU0002744274	Monoclonal antibody to rdb fragment in composition of sars-cov-2 s protein	Shakhparonov Mikhail Ivanovich Pavliukov Marat Samvelovich Antipova Nadezhda Viktorovna	Russian federation

Source: Own elaboration

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