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Declaration of Academic Integrity

I hereby confirm that I prepared this Master Thesis independently and on my own, by exclusive reliance on the tools and literature indicated therein.
The sources of other people's work have been appropriately referenced. Quotation marks are used around
materials written verbatim from other sources. The thesis has not been submitted to any other examination board.

Vienna, 25 April 2021
Moshira Abdelmajeed

Abstract

The emerge of the COVID-19 pandemic, despite the preparedness plans, scientists' warnings and foresight projects, has represented a serious challenge to the public health authorities. The urgent situation requires a swift response and practical effective solutions. In the EU where millions of people are living, a harmonised action with keen insights would be of great value. In terms of COVID-19 pandemic, one of the top priorities of public health authorities is the fulfilment of unmet medical needs. This could be ideally achieved by the Marketing Authorisation (MA) of safe, efficacious and high quality COVID-19 treatments and vaccines. The standard MA is a long process and alternative procedures should be effectively used to accelerate the procedures in case of public health emergencies.

The primary aim of this literature review is to examine available regulatory routes to grant a MA in the EU. Furthermore, to investigate to what extent will these regulatory procedures hasten the marketing authorisation of COVID-19 treatments and vaccines.
In the EU, there are several regulatory procedures for MA of human medicinal products, which were originally implemented for different scopes including unmet medical needs and authorisation of medicinal products to be used in emergency situations. These procedures such as conditional marketing authorisation, compassionate use programs and extension of MA could be of great use during the pandemic. Provisional procedures as rolling review and rapid scientific advice were designed by European Medicine Agency (EMA) to expedite the assessment stages.

The regulatory authorities in the EU, for the purpose of placing effective and safe treatments and vaccines in the market, have established several flexibilities and simplifications. Accordingly, in the period between December 2019 - February 2021 (i.e., within 15 months), a total of one medicinal product and three vaccines were officially authorised in the EU. In addition to the review of two treatments under
referral procedures aiming to support their administration in the Member States.

Abstract (Deutsch)

Die Covid-19 Pandemie stellt trotz Warnungen von Gesundheitsexperten, Krisenmanagementplänen und Prospektivanalysen eine große Herausforderung an Gesundheitssysteme weltweit dar. Die dringliche Situation erfordert rasche und effektive Lösungsansätze. Die EU, als Lebensraum vieler Millionen Menschen, würde durch ein harmonisiertes, gemeinsames Vorgehen bei der Analyse, Verarbeitung und Umsetzung der neuesten wissenschaftlichen Erkenntnisse profitieren.

Hinsichtlich Pandemien zählt es zur höchsten Priorität der öffentlichen Gesundheitsbehörden ungelöste Gesundheitsprobleme aufzudecken und zu beheben. In diesem Zusammenhang nimmt die Arzneimittelzulassung von sicheren und effektiven Arzneimitteln und Impfstoffen eine zentrale Rolle ein.

Die Arzneimittelzulassung ist normalerweise ein langwieriger Prozess, sodass alternative Strategien für die Beschleunigung dieser Verfahren in Ausnahmesituationen entwickelt werden müssen.

Das primäre Ziel dieser Arbeit ist die Beleuchtung der derzeit verfügbaren regulatorischen Mechanismen bei der Arzneimittelzulassung. Darüber hinaus soll untersucht werden, inwieweit sich diese Regulierungsverfahren auf die Zulassung von COVID-19-Behandlungen und Impfstoffen auswirken.

In der EU finden sich mehrere gesetzliche Zulassungsverfahren, einschließlich jener für die Zulassung von Medizinprodukten in Krisen des öffentlichen Gesundheitswesens. Verfahren wie bedingte Zulassung, Compassionate use programs und Erweiterung der Zulassung können in Zeiten einer Pandemie von großem Nutzen sein.

Rolling Reviews wurden hier als Instrument für die raschere Analyse und Evaluierung von der Europäischen Arzneimittelagentur (EMA) eingeführt. Die Rahmenbedingungen für Arzneimittelzulassungen auf EU-Ebene wurden diesbezüglich als Konsequenz gelockert um schnell wirksame und sichere Behandlungen, wie Impfstoffe auf den Markt zu bringen. Als Resultat dieser Maßnahmen wurden im Zeitraum von Dezember 2019 bis Februar 2021, innerhalb von 15 Monaten, demnach insgesamt 1 Arzneimittel und 3 Impfstoffe offiziell in der EU zugelassen.

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1 Introduction

Since the emerge of Coronavirus Disease 2019 (COVID-19), the world is drawing lessons from this critical and challenging situation. COVID-19 pandemic and its serious implications have emphasised the great importance of planning and preparedness for future public health crisis. Prospective support of innovative research and development of effective pandemic vaccines and medicines should be, by all means, a top priority by the health institutions all over the world. In this context, the World Health Organisation (WHO) has adopted an international strategy and preparedness plan in May 2016, namely 'the research and development (R&D) Blueprint'. This strategy aims to activate rapidly the research and development projects once an epidemic breaks out, hence accelerate the availability of vaccines, medicines and diagnostics. In order to ensure that the efforts of the broad global team of experts working under the R&D blueprint project remain focused and productive, a list of priority diseases was established. The list includes diseases and pathogens with potentials to cause a public health emergency. The "Disease X" is one of the listed priority diseases and according to WHO it represents 'the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease'. Lately, Disease X has become COVID-19 (WHO, 2020c). COVID-19 has emerged in December 2019 in Wuhan, China and has expanded within weeks all over the globe.

On 11 March, the WHO has declared the Coronavirus outbreak a pandemic (WHO, 2020e). Since then, the pandemic has and is continuing to affect enormously human lives, the economy and healthcare systems. Such public health emergencies represent a real challenge to the public health regulatory authorities and organisations, since the need to respond quickly and properly in order to spare lives and manage the crisis properly is considered a matter of high priority.

The European Union (EU), without delay was alerted by the escalating situation and the medicine regulatory authorities including European Medicine Agency (EMA), European Commission (EC) and Head of Medicine Agencies (HMA) have actively mobilised all the resources to tackle the virus. As the outbreak is continuing to intensify, a growing need for effective treatments and vaccines has appeared to be the ultimate solution.

Given that, the COVID-19 treatments and vaccines are either mandatorily fall under the scope of centralised procedure, or the pharmaceutical companies are strongly encouraged to apply for centralised marketing authorisation in order to ensure timely access of all Members States to treatments (FITT, 2020), EMA has encouraged medicines and vaccine developers to make use of already established regulatory flexibilities such as conditional marketing authorisation, accelerated procedures and compassionate use programs to accelerate the development and authorisation of potential treatments and vaccines.
Together with new regulatory activities which were specifically designed to fast-track the development and approval of such medicines and vaccines as rolling review and rapid scientific advice (EMA, 2020c).

This master thesis focuses on the available regulatory flexibilities and procedural simplification measures implemented by the health authorities in the EU, which can be of great use in terms of pandemics.
It also represents the COVID-19 treatments and vaccines authorised in the EU following the employment of such useful tools.

This paper is divided into main four chapters:
Chapter I gives a brief overview on the emerged infectious diseases (EID), their origins and their potentialities to start a pandemic. In addition to, the definitions of pandemic and examples of the known outbreaks. Finally, it discusses briefly the COVID-19 situation the EU.
The second Chapter addresses the response of the regulatory authorities in the EU to manage the medicine regulatory activities during the COVID-19 pandemic. It also discusses briefly the regulatory flexibilities established by the health authorities in Austria.
In the third chapter, an overview of the available marketing authorisation procedures and the effective tools which can be used to accelerate the approval of COVID-19 treatments and vaccines, is in full details illustrated.
The last chapter investigates the COVID-19 treatments and vaccines which has profited from the forementioned procedures and were approved for the EU market in addition to those which were reviewed under Article 5(3) by the EMA to support their administration in the Member States prior to authorisation until the end of February 2021.

2 Methodology

In order to investigate the objectives of this paper an exploratory secondary research based on literature review was conducted. Relevant data on the body of the research, published mainly between December 2019 and February 2021, was reviewed and collected from online resources (scientific articles, publications, e-journals, clinical studies) using online search engines as Pubmed and Google Scholar in addition to licensed and open access databases service provided by the Vienna University Library.

External data including official statements, guidelines, EU legislations and regulatory procedures was extracted from EU government sources mainly EMA and EC websites besides other official websites of the EU, UK, Austria and other Member States.

Since the information about COVID-19 is considered new and the situation is continuously evolving, several updates, revisions and provisions were observed during the research time. Eventually, a reformation of the work to include the updated knowledge was, where feasible, carried out.

3 Definitions, Examples of pandemics and the current situation of COVID-19

3.1 Definitions of pandemics

Emerging Infectious Diseases (EID) and their risk to trigger disease outbreaks in the future are a global health concern that need to be prioritised by public health authorities as well as infectious diseases experts and scientists. Studies suggest that about 177 human pathogens are considered emerging or remerging, whereby the majority (around 60%) are of zoonotic origin (Taylor, Latham and Woolhouse, 2001; Woolhouse and Gowtage-Sequeria, 2005). Zoonosis is '*an infectious disease that has jumped from a non-human to humans*' (*WHO Zoonoses*, 2020). The frequency of emerging of such zoonotic infections, known and novel ones, is increasing alarmingly in the last few years, considering that many of these infections have caused major outbreaks such as Ebola, Avian/Swine Influenza and recently Coronavirus Disease 2019 (COVID-19). Hence, there has been considerable interest in understanding the aetiology and diversity of zoonotic infections and in enhancing the preparedness for future candidates that are potentially able to cause a pandemic (Wilcox and Gubler, 2005; Cascio *et al.*, 2011; Karesh *et al.*, 2012; Rabaa *et al.*, 2015).

A growing body of literature has investigated the known EIDs, their global trend patterns, origins, frequency of emergence and re-emergence, transmission and their underlying drivers. These key drivers such as travel and tourism, natural environment, climate and global trade are epidemic indicators and serve as an early alarming system in Europe and around the world (Woolhouse and Gowtage-Sequeria, 2005; Jones *et al.*, 2008; Suk, Lyall and Tait, 2008; Semenza *et al.*, 2013, 2016; Semenza, 2015). An early warning system could be helpful to identify potential pandemics.

Based on the hypothesis that Western Europe is one of the hot spots for EIDs and that the European Union is highly connected to other hot spots (Jones *et al.*, 2008), a number of foresight programs and studies were initiated. In 2008 the European Centre of Disease Control and Prevention (ECDC) has conducted a foresight project. The project´s main aims were

first to overview the key drivers that will affect the transmission of EIDs in the European Union by 2020 and second to discuss the likely infectious disease threats and the capability of the EU to cope with them (Suk and Semenza, 2011). Such foresight programs are of great value for public health authorities and decision makers in the EU as they provide a guidance for better proactive preparedness and response planning for the next potential pandemic (Office of Science and Innovation, London, 2006; Suk, Lyall and Tait, 2008; Suk and Semenza, 2011).

The term pandemic origins from the Greek **pándēmos**: Pan (all) and demos (people, public) (Definition of PANDEMIC, 2020).
On one hand pandemic is defined in the dictionary of epidemiology as follows: "an *epidemic occurring over a very wide, crossing international boundaries, and usually affecting a large number of people. Only some pandemics cause severe disease in some individuals or at a population level. Characteristics of an infectious agent influencing the causation of a pandemic include: the agent must be able to infect humans, to cause disease in humans and to spread easily from human to human*". (Porta, 2014).
On the other hand, the World Health Organization (WHO) definition of pandemic is brief and simple namely '*A pandemic is the worldwide spread of a new disease'* (WHO, 2010b).

3.2 Examples of the known documented disease outbreaks

Global disease outbreaks are in fact not a new phenomenon, in the recorded history human existence was several times challenged by deadly pandemics where the impact of such outbreaks was enormous at that time. Some examples of the most devastating well-known pandemics are presented below.

- **The plague (1347-1351)**

Also known as Black Death, caused by bacterial infection with *Yersinia pestis* and considered to be the most fatal documented pandemic in history. The Black Death has emerged in the 14th century and is believed to be responsible for the death of more than 50 million humans, about one third of the population, in Europe (Bassareo *et al.*, 2020; Chaikhouni, 2020).

♦ Cholera (1817- present)

In 7 major outbreaks over the last centuries cholera was widely spread all over the world. The disease, caused by bacteria called *Vibrio cholerae,* was first originated in Asia and then subsequently extended to Europe. Several Cholera outbreaks have caused the death of millions and the death toll is still rising as the seventh outbreak continues until our present time despite the availability of a safe and effective vaccine (Lippi, Gotuzzo and Caini, 2016; Chaikhouni, 2020; Deen, Mengel and Clemens, 2020).

♦ Influenza pandemics

The historical records of influenza pandemics are huge and extended over centuries. The threat of influenza is still a global health challenge. As matter of fact there are great concerns among the health care community regarding the next influenza pandemic as the number of novel influenza A infections in humans have raised sharply over the last years.

◊ Spanish Influenza (1918-1919)

The 1918 pandemic was spread globally through 3 waves. The first wave of the Influenza pandemic has emerged in USA and expanded within 9 months across the globe. The death records of this catastrophic event range from 20- 22 million and up to 100 million deaths with remarkable high mortality among young adults. As a consequence, the life expectancy rates in Europe were noticeably affected. The Spanish flu cause has been later identified as H1N1 virus, a zoonotic virus (avian influenza virus) that has mutated and was capable to infect and transmit among humans (National Academies of Sciences *et al.*, 2019; Chaikhouni, 2020).

◊ H1N1 flu (2009-2010)

The H1N1 influenza pandemic, also known as swine flu, was first detected in 2009 in Mexico after a zoonotic influenza virus passed from pigs to humans and due to mutation has transmitted among humans. According to WHO´s report more than 18.500 confirmed cases died. (WHO, 2010a). Where the WHO regional office for Europe has suggested a death toll

between 100.000 and 400.000. Similar to 1918 influenza pandemic, the younger population was hit the hardest while the older generations were spared (National Academies of Sciences *et al.*, 2019).

♦ Coronavirus outbreaks

Coronaviruses belong to a large RNA virus family known to cause mild respiratory as well as gastrointestinal infections, however the highly pathogen strains can trigger severe acute respiratory symptoms. Many of recently identified strains have proven to be novel, zoonotic with high potential to adapt humans as host. Noteworthy, 3 of 7 known coronaviruses have provoked a global outbreak (Channappanavar and Perlman, 2017; Liu, Kuo and Shih, 2020; Park, Thwaites and Openshaw, 2020).

◊ Severe Acute Respiratory Syndrome Coronavirus (SARS-COV) (2002-2003)

First emerged in 2002 in China, where atypical pneumonia-like symptoms were reported. The highly contagious virus has travelled then with the infected passengers, spreading the disease to other continents (Baric, 2008; De Wit *et al.*, 2016).

With more than 8000 reported cases including 813 deaths in 27 different countries (WHO, 2003a), the SARS pandemic was declared to be over by WHO on 5 July 2003 (WHO, 2003b).

◊ Middle East Respiratory Syndrome Coronavirus (MERS-COV) (2012)

In 2012, a novel coronavirus has struck the Arabian Peninsula in the middle east. The virus causes a severe pneumonia and has a high mortality rate with limited possibility for human-human transmission (Zaki *et al.*, 2012; De Wit *et al.*, 2016; National Academies of Sciences *et al.*, 2019). About 27 countries worldwide have reported 858 deaths of MERS confirmed cases to WHO during the outbreak (WHO, 2020d). Both SARS and MERS have been indicated as a source of nosocomial outbreaks (Guarner, 2020).

3.3 Coronavirus disease 2019 (COVID-19) (2019 till present 2021)

Again, a novel, zoonotic coronavirus, namely Severe Acute Respiratory Syndrome Coronavirus 2(SARS-COV2), has jumped to humans and triggered the latest pandemic in December 2019. The disease was initially reported in Wuhan, China, when clusters of patients were diagnosed with pneumonia of unknown cause (Zhu *et al.*, 2020). Furthermore, scientists highly suggest that bats and wild animals are the animal hosts of this novel strain (Adhikari *et al.*, 2020; Liu, Kuo and Shih, 2020; Zhu *et al.*, 2020). Recently, a WHO´s experts report based on a study conducted to identify the origins of SARS-COV2 has concluded that, the emerging of the virus is likely to very likely introduced through an intermediate host (bats and pangolins) whereas the laboratory leakage hypothesis was considered to be an extremely unlikely route of introduction (WHO, 2021c).

The highly contagious virus has spread within a few weeks all over the globe representing a serious health challenge. The virus has demonstrated to transmit via respiratory droplets, contact and aerosols (Adhikari *et al.*, 2020; La Rosa *et al.*, 2020).

In most of the cases, related symptoms vary from no to mild symptoms. A study has suggested that about 80% of COVID-19 positive patients had no or mild symptoms that is why all officially reported numbers of confirmed cases and deaths could be subject to underestimation (Sumanth Khadke *et al.*, 2020). Similar to SARS and MERS, a COVID19 infection can escalate and cause an acute respiratory distress syndrome (ARDS) which is associated with higher fatality rates (Rothan and Byrareddy, 2020).

Many studies were conducted to understand the progress of the disease, the tendency to develop more serious symptoms and the severity and mortality of COVID-19. There is strong evidence which correlates the high mortality with possible risk factors such as: older age, co-morbidities (Hypertension, cardiovascular diseases, asthma), male gender or being a health care worker (Davies *et al.*, 2020; ECDC, 2020; Grasselli *et al.*, 2020; Huang *et al.*, 2020). A study in Italy has manifested worse outcomes in elder males with comorbidities (Riccardo *et al.*, 2020). Other factors like ethnicity, genetics and smoking are also under investigation (sciensano, 2020).

A timeline corresponding to of the significant events related to COVID-19 in the period between December 2019 - February 2021

31 December 2019 the virus first reported in Wuhan, China.

9 January 2020 COVID-19 cause is officially identified to be SARS-COV 2.

24 January 2020 first reported case in Europe in France.

30 January 2020 WHO declares COVID-19 outbreak a public health emergency of international concern (PHEIC).

1 February 2020 the disease is officially named COVID-19.

22 February 2020 spread of the virus in northern Italy.

26 February 2020 first reported case in Austria.

11 March 2020 WHO declares COVID-19 as a pandemic.

13 March 2020 Europe is the epicentre of the pandemic

28 April 2020 63% of global mortality from the virus is in Europe.

31 July 2020 Veklury (remdesivir) is granted a conditional marketing authorisation. First treatment for COVID in the EU.

14 December 2020 a new variant of SARS-COV2 is identified in UK.

21 December 2020 first vaccine (mRNA vaccine, developed by BioNTech and Pfizer) is conditionally authorised across EU.

6 January 2021 European Commission (EC) authorises the COVID-19 vaccine Moderna in the EU.

29 January 2021 Conditional Marketing Authorisation of Vaxzevria (COVID-19 Vaccine AstraZeneca) in the EU.

(EC, 2020b, 2020a; WHO, 2020b; WHO/Europe, 2020; Wu *et al.*, 2020; EC, 2021; PINHO, 2021d)

The COVID-19 situation by numbers

As of 21 April 2021, the total confirmed cases of COVID-19 worldwide according to the latest WHO coronavirus disease (COVID-19) Dashboard were **142,238,073** including **3,032,124 deaths** (2021d).
As stated by the ECDC in its weekly COVID-19 situation update (15 April 2021), a total of **28,496,538 cases** including **645,412 deaths** in EU/EEA and UK have been reported (2021).

The AGES COVID19 Dashboard has as well published the latest updates of the COVID situation on 21 April 2021 in Austria as follows: **596,434** laboratory confirmed cases and **9,749** deaths with a total of **29,335,166** performed tests (2021).

Fact is that the globally reported cases are likely fractions of the actual numbers of infections, indeed more recent evidences have shown that the true infection rates could be up to 10 times the rates estimated from the reported numbers and that the virus is much more widely spread through the undetected cases (Bohk-Ewald, Dudel and Myrskylä, 2020; Li *et al.*, 2020; Phipps, Grafton and Kompas, 2020; Seth Flaxman, Swapnil Mishra, Axel Gandy et a, 2020; Wu, Leung and Leung, 2020; Manski and Molinari, 2021).

A study conducted in April 2020 in Austria has estimated that about 0.33% of the Austrian population were infected during the study period (about 28,500 individuals). Moreover, the study has suggested that the proportion of positive cases by 95% Confidence Interval ranges between 10,200 and 67.400 individuals in absolute terms (Ogris and Oberhuber, 2020).
The underestimation of the numbers is believed to be due to multiple reasons, for example subclinical manifestations or asymptomatic infections, false negative test results, inadequate testing capacity, incorrect testing procedures or inaccurate testing timeframe in addition to unreported cases (Böhning *et al.*, 2020; CDC, 2020; Phipps, Grafton and Kompas, 2020).

4 Response to COVID-19 pandemic and Regulatory measures established by public health authorities in the EU regarding COVID-19 treatments and vaccines

The regulatory authorities responsible for the regulation of human medicinal products in the EU/EEA on the first line are the European Commission (EC), European Medicine Agency (EMA) and Head of Medicine Agencies (HMA). These organisations, besides other EU agencies and the National Competent Authorities (NCA), operate jointly as a network to manage the regulatory activities in the EU (Head of Medicine Agencies, no date).

This chapter gives a brief overview on some of the regulatory modifications done by the public health authorities in the context of COVID-19 vaccines and treatments, namely EC, EMA, HMA, the European Directorate for the Quality of Medicines (EDQM) and the Austrian Federal Office for Safety in Health Care (BASG) in Austria.
The ultimate purpose of these regulatory actions is to facilitate and focus attention on the marketing authorisation (MA) of human medicinal products and vaccines for the treatment of COVID-19 while simultaneously maintaining the quality, safety and efficacy of the medicines and vaccines (HRABOVSZKI, 2020d).
A number of these reasonable actions are listed below.

4.1 The response of the European Agencies

4.1.1 COVID-19 EMA Pandemic Task Force (COVID-ETF)

The EMA´s Task Force key role is to help the national competent authorities in the Member States and the European Commission to implement rapid and coordinated decisions concerning the development, authorisation and monitoring of treatments and vaccines for COVID-19.
Some of the Task Force´s activities include:

- Assessing the convenient scientific data on potential COVID-19 treatments and distinguishing promising candidates.

- Providing scientific support in cooperation with the Clinical Trials Facilitation and Coordination Group (CTFG) to facilitate the clinical trials of the potential COVID-19 treatments which are conducted in the European Union.
- Acting as peer reviewer and as forum for discussion through the evaluation of the rolling data review in product related assessments.

It is noteworthy that the Task Force is supervised by EMA´s Committee for Medicinal Products for Human Use (CHMP) in all its activities. (CZARSKA-THORLEY, 2020a; European Medicines Agency, 2020a).

4.1.2 EMA health threats plan

The health threats plan describes the response of the Agency in case of serious public health crisis. Furthermore, the plan covers vital operational procedural aspects whereby a series of procedures is highly recommended under such circumstances, for example procedures for rapid scientific advice on the potential treatments under development and procedures for fast-track approval of vaccines and medicines intended for the prophylaxis and treatment of an emerging health threat via centralised authorisation procedures.
The plan has come into force on 4th February 2020 in response to COVID-19 outbreak (European Medicines Agency, 2018; Awan, 2020).

4.1.3 The European medicines regulatory network COVID-19 business continuity plan

The plan sets out the principles to ensure that the public health authorities in the EU continue to manage their main basic regulatory activities during the COVID-19 pandemic by which the public health comes in the first place. Moreover, the plan includes specific measures which are implemented to handle and prioritise all regulatory activities and procedures related to COVID-19 treatments and vaccines (European Medicines Agency, 2020b; HRABOVSZKI, 2020d).

4.1.4 The role of the Committee for Medicinal Products for Human Use (CHMP)

Some of the activities in which the Committee is devotedly involved, are:

- CHMP evaluates applications for marketing authorisation or conditional marketing authorisation as well as starts rolling reviews for potential COVID-19 vaccines and treatments (CZARSKA-THORLEY, 2020d; PINHO, 2020a, 2020c).
- It provides recommendations, updates and assessment reports in the context of COVID-19 vaccines and treatments (FRANCISCO, 2020; CZARSKA-THORLEY, 2021a, 2021c).
- It issues positive opinions on COVID-19 vaccines and therapies that show sufficient robust data on safety, effectiveness and high quality (PINHO, 2020b).
- CHMP has Published a statement on 16 March 2020 urging the EU research society to pool research resources and establish large randomised controlled clinical studies in which all Member States are encouraged to participate (HRABOVSZKI, 2020a).

4.1.5 The EU strategy for COVID-19 vaccines

The European Commission has adopted on 17 June 2020 an EU strategy to accelerate the development and MA for COVID-19 vaccines and to ensure their availability while keeping quality, safety and efficacy standards. One of the two fundamental principles which the strategy is based on, is to adjust the EU´s regulatory systems to the current emergency and to take full advantage of the existing flexibilities with the aim of hastening the approval´s process, and hence the availability of safe, high quality and effective COVID-19 medicines and vaccines. This particular principle emphasises the importance of sufficient relevant data to ensure the safety of patients. Furthermore, it suggests a number of temporary measures including early engagement with EMA, accelerated procedures, flexibility in the requirements of labelling and packaging and the temporary derogation from genetically modified organisms (GMO) Directive (De Keersmaecker and Cassidy, 2020; European Commission, 2020).

4.1.6 Additional regulatory flexibilities and guidance provided by EU Health Institutions for applicants and Marketing Authorisation Holders (MAH)

- **'Notice to stakeholders: Questions and answers on regulatory expectations for medicinal products for human use during the COVID-19 pandemic'**

The guidance addresses the regulatory challenges expected due to the pandemic with particular emphasis on the medicines and vaccines essential to treat COVID-19 patients. Some of the important themes covered by the guidance are:

- Marketing authorisation and regulatory procedures.

- Quality variations and changes in context of manufacturing, supply chains, GMP and GDP issues. For example, what is termed Exceptional Change Management Process (ECMP) which was exclusively made available for medicines needed to treat COVID-19 patients. This tool allows exceptionally the MAHs to swiftly carry out changes of manufacturing/control sites or supply chains that are not originally mentioned in the MA´s dossier. Consequently, it minimizes the risk of shortages of such medicines in the EU (European Medicines Agency, European Commission, and Head of Medicine Agencies, 2020b).

An additional version: '**Practical guidance of the CMDh for facilitating the handling processes during the COVID-19 crisis'** was also compiled by the Co-ordination Group for Mutual Recognition and Decentralised Procedures - human (CMDh) to give further explanation of the notice on the handling of MR (Mutual Recognition)/DC (decentralised) procedures (CMDh, 2020).

- **'Guidance on the management of clinical trials during COVID-19 pandemic'**

This document´s aim is to provide a set of harmonised simplification measures which are highly recommended to be implemented EU-wide so that clinical research in Europe would be properly maintained and not disrupted during the COVID-19 pandemic (European Medicines Agency, European Commission, and Head of Medicine Agencies, 2020a).

- An updated version of **e-Submission Gateway user interface** which enables applicants to flag submissions related to COVID-19 and thus help EMA to quickly recognise and prioritise such submissions. (European Medicines Agency, 2020c)
- Supportive initiatives which are provided by the European Directorate for the Quality of Medicines and Healthcare (EDQM) in the context of COVID-19 vaccines and

therapies. The EDQM offers for a limited time free access to relevant quality standards and guidance such as 'updated European Pharmacopoeia vaccines package for COVID-19 vaccine developers', 'CEP fast-track procedures for the active substance of interest for COVID-19 therapies' and 'European and British supportive pharmacopeial texts relevant for antiviral medicines' (EDQM, 2020b, 2020d, 2020e, 2020a, 2020c).

4.2 The response of the health authorities in Austria

The Austrian Federal Office for Safety in Healthcare (BASG) has as well introduced some regulatory flexibilities to ensure the availability of crucial medicines for COVID-19 patients.

- Handling of expired medicinal products essential for COVID-19 patients during the pandemic.

According to special provision for the medicinal products in time of COVID-19 pandemic, the marketing authorisation holder is allowed, under certain conditions, to apply for extended handling of expired crucial medicines. Such applications are restricted for crucial COVID-19 medicines administered in hospitals to avoid their shortage and only during the period of the pandemic. The submitted applications would be processed then free of charge by BASG. (BMASGK, 2020; Bundesamt für Sicherheit im Gesundheitswesen, 2020).

- Further measures employed by BASG to mitigate medicines shortages.

In times of crisis the BASG is delegated by the Federal Ministry of Labour, Social Affairs, Health and Consumer Protection (BMASGK), in accordance with the Austrian Medicinal Products Act (AMG) to take the following actions:

- Investigate the reasons behind the shortage and report this information to the involved authorities.
- Share the information regarding the extent of the shortage with stakeholders as well as inform the MAH of the corresponding information.
- Notify other (NCA) and/or EMA to communicate the information.
- Prioritise the new MA´s applications or the extension of MA for COVID-19 medicinal products if it is believed to likely mitigate the supply shortage of such medicines, or

rather encourage an accelerated assessment via European procedures (BASG, 2020).

There is no doubt that the role of health regulators either on EU level or as NCA is particularly critical in the current emergency, as the need of safe and effective COVID-19 treatment is really urgent. Under such circumstances, the regulatory authorities should make a compromising risk-based decision whereby the balance between the urgency and the public safety is as possible preserved. Reliable robust data, transparency, international cooperation, strategic coordination between global medicine regulatory authorities and optimised surveillance approaches seem to be of particular significance to govern the critical situation.

5 Overview of EMA´s rapid formal review procedures concerning COVID-19 treatments and vaccines

In 1995 the European Medicines Agency was established to foster the scientific skills experience in the evaluation, supervision and monitoring of medicines in order to protect public and animal health across Europe. This key goal was successfully achieved over the years due to the unique regulatory system adopted by the Agency. In fact, the European regulatory system is based on cooperation between about 50 NCAs headed by HMA, EC and EMA known as the European medicines regulatory network. The network´s concept imparts a very effective exchange of knowledge, scientific expertise and best practices aiming to provide the highest quality of medicines regulation. Actively, EMA and its seven committees are dedicated for the cause of ensuring safety and efficacy of the medicines throughout the EU/EEA (EMA, 2016b; European Medicines Agency, 2018b).
One of the main responsibilities of EMA and the CHMP is the evaluation of centralised Marketing Authorisation Applications (MAA) for human medicinal products. Via centralised procedures a medicinal product is authorised in all EU Member States as well as Iceland, Norway and Liechtenstein (EMA, 2018e).

Since the emerge of the COVID-19 pandemic and the Agency including its committees and related working groups are on high alert and working cooperatively at full capacity to cope with this challenging situation.
As soon as the SARS-COV2 outbreak has been declared a public health emergency of international concern, EMA has immediately activated its plan for managing health threats.
Furthermore, EMA has invited developers of potential treatments or vaccines to contact the Agency and take advantage of the available supporting measures which can facilitate the development and approval of such therapies as rapid scientific advice, conditional marketing authorisation, PRIME scheme, accelerated assessment.
EMA has also started searching the landscape for promising antivirals or vaccines as well as analysing all relevant information on pharmaceutical companies´ drug pipelines (HRABOVSZKI, 2020c).

Principally EMA is focusing on the following aspects, which is regularly updated in order to ensure the safety of the public across the EU:

- Guidance for developers and other stakeholders of potential COVID-19 treatments and vaccines.
- Availability of medicines at the time of COVID-19 pandemic.
- Public health counselling during COVID-19 pandemic.
- Support of development of COVID-19 treatments and vaccines.
- Working closely with other EU and international partners as well as participating effectively in the strategic meetings and the regulatory workshops under supervision of the International Coalition of Medicines Regulatory Authorities (ICMRA) (HRABOVSZKI, 2020b).

On 4 May 2020 '**EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines**' was published and considered as procedural guide for the developers of COVID-19 therapeutics and vaccines. The document outlines the flexibilities in number of review procedures related to COVID-19 including rapid scientific advice, rapid agreement on a paediatric investigation plan (PIP) and rapid compliance check, rolling review, conditional marketing authorisation, extension of marketing authorisation, compassionate use and other procedures as PRIME scheme and accelerated assessment (EMA, 2020c).

This chapter highlights the aspect '**Guidance for developers and companies on COVID-19 treatments and vaccines**' and provides an overview of the regulatory pathways established by EMA to accelerate the development and evaluation activities and thus, the marketing authorisation of medicinal products and vaccines for COVID-19.

5.1 Conditional Marketing Authorisation (CMA)

In 2006, CMA was introduced in the European Union by the EU legislation '(EC) No.507/2006 on legal basis of regulation (EC) No 726/2004'.
According to the Commission Regulation, conditional marketing authorisation is a route to grant a marketing authorisation on the basis of less comprehensive data though subject to specific obligations for medicinal products that fulfil unmet medical needs (EC, 2006). In other words, it is a pathway to endorse an early access of patients to medicines that fulfil an unmet medical need. The pragmatic tool allows the fast-track approval of medicines which comply with a set of conditions:

- The benefits of this medicine outweigh the risks.
- The applicant will continue to provide the clinical data post-authorisation.
- The medicine fulfils an unmet medical need.
- The urgent availability of such medicines to patients takes precedence over the risks implied due to the incomplete comprehensive data (EMA, 2018c).

Principally, the uncertainties due to the absence of comprehensive data within the assessment of CMA should be compensated by keeping the uncertainties arising from further parts of the application dossier to a minimum. Accordingly, a comprehensive set of non-clinical and quality data should be exhaustively available whereas the clinical data could be less comprehensive to grant a CMA. With one exception, namely for products to be used in the context of emergencies due to public health threats or pandemics, where a CMA could be eventually granted even though the preclinical or pharmaceutical data are incomplete. Such applications will be thoroughly evaluated on a case by case basis, by which the benefits and the urgency of the medicinal product versus the risks associated with lack of data should be carefully weighed (EMA/CHMP, 2016).

Noteworthy that the application for CMA is reserved for medicinal products that fall within the scope of the Commission Regulation which includes:

- medicinal products intended for the prevention, treatment or diagnosis of debilitating or life-threatening diseases,

- medicinal products classified as orphan drugs,
- medicinal products meant for a public health emergency (e.g., a pandemic) recognised by WHO or the competent authorities in the EU (EC, 2006).

On the assumption that a medicine fulfils the criteria set out in the forementioned Regulation, a CMA may be requested by the applicants or rather proposed by the CHMP. However, very restrict post-authorisation obligations and commitments such as completing ongoing studies or starting new studies, collecting additional relevant data, providing a resilient risk-management and safety monitoring plan and legally binding conditions for MAH should be accomplished within specified timelines. The specific obligations imposed by CHMP should guarantee first, that the benefit-risk balance of the related indication remains positive and second, that the incomplete clinical data will be timely provided. For transparency reasons, the specific regulations and the timelines for their completion will be predetermined in the CMA and will be published by the agency in the **European Public Assessment Report (EPAR)**.

The CMA is, thereafter, valid for one-year renewable which could be then eventually converted to a standard marketing authorisation also known as 'marketing authorisation not subject to specific obligations', once all obligations have been fulfilled and the corresponding clinical data has proved the fact that the medicine is safe, effective and of high quality. Otherwise EMA has the authority to suspend or annul the MA (EMA/CHMP, 2016; EMA, 2018c).

A number of studies have found that medicines granted conditional authorisation, despite the lack of clinical data, were considered as safe as medicines authorised with standard marketing authorisation and they have triggered neither post-marketing safety vigilance nor safety related withdrawals. This may be referred to first, the restricted post marketing surveillance system adopted by the Agency including:

- Rigorous EU-risk management plan,
- Additional and proactive pharmacovigilance tools,
- Periodic safety update reports which should be immediately submitted on request of the Agency or at least every six months and

- Further studies conducted as part of the specific obligations to maintain a positive benefit-risk balance.

Second, the reluctance of the regulatory authorities to withdraw medicinal products that fulfil unmet medical need or those which have no alternative, instead these agencies might rather to administer a DHPC (Direct Healthcare Professional Communication). A serious safety issue is defined as an issue that activates a regulatory action in form of either a DHPC or a safety-related withdrawal of the CMA.

Third, the real-life use of such medicines usually involves a small number of patients making the chance to detect less common serious adverse effects, is quite low (Boon *et al.*, 2010; Heemstra *et al.*, 2010; Arnardottir *et al.*, 2011; Blake *et al.*, 2011; Hoekman *et al.*, 2015).

The granting of CMA, its renewal and all related arrangements and requirements are fully detailed in EMA´s guidance:

"Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human falling within the scope of Regulation (EC) No 726/2004".

The guideline shall be deemed as a reference for the applicants who have interest in CMA. It also emphasises the importance of seeking a CHMP scientific advice or protocol assistance before the submission of the MA application as a key procedure to acknowledge the best beneficial strategy to merit a positive opinion (EMA/CHMP, 2016; EMA, 2018c).

In 2016 EMA has published a ten-year report on the CMA to summarise the agency experience with this type of MA applications. The report represents the outcomes of analysing data collected over ten years and interprets them in different aspects giving an approximate perception of this regulatory tool. Some of the noteworthy findings outlined in the report were for example:

- More than a half of CMA granted were in oncology area followed by about one third for infectious diseases.
- Clinical studies included in the initial application were indeed mostly phase II or phase III.

- In most cases, the specified obligations were in context of submission of final results from clinical studies of different phases.
- Only a limited number of specific obligations needed an extension over its due time which could reflect a diligent strategy by CHMP, consenting only to uncompromising timelines at the beginning and accepting more flexibility only if a reasonable justification was submitted by the applicants.
- The merging of conditional authorisation and the accelerated assessment procedure seemed to be beneficial, thereupon the use of both tools was highly recommended in the revised version of the CHMP guideline.
- Submission of the specific obligations results, where a significant delay was observed, was very limited and the compliance with the timelines was in general acceptable.
- More than half of the medicinal products which were granted a CMA have received either CHMP scientific advice or protocol assistance before submitting the initial application. Likewise, products that followed the CHMP scientific advice were more likely to grant a CMA.
- Products that have fulfilled all imposed specific regulations in due time were able to grant MA on average 4 years earlier in comparison to duration in which a standard MA could be granted. This outcome reinforces the main scope of the CMA, promoting an early access to crucial medicines for the patients who are in need (EMA, 2016a).

During the COVID-19 pandemic and due to the urgent need for treatments and vaccines, CMA was recognised as a powerful tool and the procedure of choice to grant swiftly a marketing approval as soon as relevant data establishing evidence of a positive benefit-risk balance becomes available, alongside with the commitment to complete specific regulations and post-authorisation binding conditions.

The assessment of promising medicines and vaccines was given an additional boost using the **rolling review** of data once they are available. The coupling of both tools was by all means of great value, specifically for COVID-19 vaccines(EMA, 2018c).

As of February 2021 three vaccines against COVID-19 (COVID-19 Vaccine AstraZeneca, COVID-19 Vaccine Moderna and Comirnaty) as well as one antiviral medicine (remdesivir) were conditionally authorised in the EU (GLANVILLE, 2021b).

5.2 Accelerated assessment

Accelerated assessment is a further useful procedure which could be considered by developers of potential treatments and vaccines in emergency situations. Adopted in 2006 by article 14 (9) of EU regulation (EC) No 726/2004. In addition to recital 33 of the very same regulation where the scope of accelerated procedure is defined as:
"in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, **accelerated assessment** procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions". Accordingly, the applicant of medicinal products which fall within the scope provided by the EU legislation may admit a request for an accelerated assessment procedure. The request shall be properly justified and eventually will be evaluated by the CHMP on case-by-case basis. In case the CHMP accepts the request, the MAA shall be evaluated in 150 days (in addition to one month clock stop) instead of 210 days (the standard time frame, without clock stops, for the evaluation of centralised marketing authorisation) as foreseen in Article 6(3) by the Regulation (EC) No 726/2004 (European Parliment and The Conuncil, 2004).
The justification should include rationale evidence supporting the claim that this particular medicinal product is of major therapeutic interest and that, it covers substantially the unmet medical needs, hence supports and improves the public health in the EU.

EMA guideline **"Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004"** is designed by CHMP to provide applicants with necessary instructions to properly request an accelerated assessment procedure and they should abide by its content unless otherwise is justifiable.

For an effective usage of the accelerated assessment procedure, EMA strongly recommends a pre-submission meeting with the agency and rapporteurs from CHMP, Pharmacovigilance Risk Assessment Committee (PRAC) and any other involved committees as early as possible. In such meetings the applicants can discuss details of their request for accelerated assessment procedure including the available set of data and the risk management plan. Accordingly, a medicine of major therapeutic interest, with the aid of PRIME scheme, is likely eligible for accelerated assessment by the time of application.

As a second step, the applicant should submit a formal request for an accelerated assessment 2-3 months before the submission of the routine marketing authorisation application. That is to say, the request including the form, the justification in addition to accurate and representative details regarding GMP and GCP aspects should be sent electronically to EMA. The early submission of relevant information about manufacturers and their activities, GMP compliance, pivotal clinical studies and related GCP inspections is necessary in order to integrate the standard GCP inspections together with preapproval GMP inspections into the accelerated assessment timetable. The request would be then evaluated, for the applicability to an accelerated assessment, by the rapporteurs. The CHMP will take a decision based on the submitted evidence and the recommendations of the rapporteurs. The CHMP opinion will be communicated to the applicant and the explanation for rejecting or accepting the request will also be briefly presented in the CHMP assessment report.

Provided that, the request for an accelerated assessment is granted, the CHMP shall follow the accelerated timetable for the assessment as long as the objective of the accelerated procedures is chiefly preserved. Otherwise the CHMP has the authority to revoke, at any time, the accelerated assessment and continue the evaluation of the application according to the standard timelines of centralised procedure (EMA, 2016c, 2018a, 2020e).

A cohort study was conducted in 2016 to compare the new molecular entities (NME) approved by EMA and FDA after an accelerated review time and to investigate the added therapeutic value of such medicinal products has concluded that EMA is more selective and restrictive than FDA regarding granting a medicinal product an accelerated assessment request. This selectivity might be attributed to the fact that EMA reserves this procedure for the promising products of major therapeutic value. A second reasonable explanation is that EMA and its CHMP can acknowledge at any time during the assessment of the MA

application that the accelerated assessment is no longer relevant and decide to continue the evaluation under the standard assessment time frames. The study has also revealed that EMA has considered its accelerated assessment procedure mainly for two therapeutic categories, namely antineoplastic and immunomodulators drugs and systemic anti-infectives (Boucaud-Maitre and Altman, 2016).

In September 2020 EMA has received an application for authorisation of Dexamethasone Taw, for treatment of hospitalised COVID-19 adult patients. The CHMP has started the evaluation of the application based on an accelerated assessment timetable (CZARSKA-THORLEY, 2020d).

5.3 Compassionate use programs (CUP)

Compassionate use program is an opportunity for patients with severe or life-threating condition to access promising unauthorised medicinal products that fall within the scope of Article 3 (1) and (2) of Regulation (EC) No 726/2004. Patients with unmet medical needs or who cannot participate in clinical trials can benefit from compassionate use programs. The principles of such programs are laid out in Article 83 (1) of Regulation (EC) No 726/2004 (European Parliment and Council of European Union, 2004). The Regulation introduces the legal basis of compassionate use in the EU for medicinal products which are eligible for the centralised procedure however, the implementation and approval of these programs remains within the competence of the Member State.

The Regulation further encourages the Member States to notify the Agency if they intend to make a medicinal product available for compassionate use. Furthermore, the Member States may seek the opinion of the CHMP with regard to the conditions for use and distribution of medicines for compassionate use as well as the targeted patients who may benefit from them. Correspondingly, the Committee would consider providing an opinion in case the same compassionate use program was notified by a number of Member States. The CHMP recommendations are valid for all EU Member States yet, not legally binding and do not replace the national legislation. An updated list of opinions adopted by CHMP and its recommendations on compassionate use is available on the EMA website, hence keep

the patients in need as well as medical doctors informed with relevant compassionate use programs.

According to Article (83) only unauthorised medicinal products which fulfil specific criteria are allowed to be put in place for Compassionate Use programs:

- The medicine which is expected to be helpful for **'patients with a chronically or seriously debilitating disease, or a life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product'**
- The compassionate use program is aimed for **a group of patients**.
- The medicinal product is currently either **undergoing clinical trials** or has already a centralised marketing authorisation application **under evaluation**.
- Pursuant to the Article (83), the EU Regulation is not applicable to medicinal products which are not suitable for the Centralised Procedures, those which already were granted a marketing authorisation via Centralised Procedure or to named patient programs (EMA, 2007, 2010, 2018b).

On a national level, the competent authority has to govern individually the assessment and authorisation procedures for compassionate use programs. Accordingly, managing a number of important aspects rest with the national competent authority such as:

- Criteria for the inclusion of patients, for example for a patient to be included in a compassionate use program a corresponding clinical trial is not available or the patient does not meet the criteria to join it.
- Scientific evidence supports the positive benefit-risk ratio including the clinical trials results.
- Reporting of adverse events and pharmacovigilance.
- Determination of the responsibilities of the involved parties in a compassionate use program (Sou, 2010; BASG, 2017).

In case a physician identifies a promising medicine that could help his seriously ill patients or wish to register them to join an active compassionate use program, he should contact the competent authority in his country. Usually, the physician or the sponsor (whether a

manufacturer or applicant for a MA) needs to make a request to grant an approval for compassionate use whereby the legal responsibility lies with the treating physician.

As a further step toward more harmonised framework in the EU, EMA has published the following guidance:

- "**Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) No 726/2004, which provide recommendations on the criteria and the procedures for compassionate use programs for Member States"**
- "**Questions and answers on the compassionate use of medicines in the European Union, which describe the setup of compassionate use programs in the EU and the role of EMA and its Committee in these activities"**

Cohort compassionate use programs benefit principally a **group of patients** upon a request from either a treating physician or a pharmaceutical company to the national concerned authority.
The applicant for a compassionate use program should submit, in accordance with national legislation, a treatment protocol and further required documents and commitments. In practice, the Cohort CUPs are established regularly by the time of submission of MAA.
Usually when relevant data from phase III are not readily available, adequate results from phase II may be in certain conditions accepted. After careful assessment of the request, treatment protocol, reliable data and reasonable justification for a CUP application an authorisation of a medicine for a limited time for a defined group of patients could be granted.
The national authority keeps a record of the participating patients and establishes a monitoring system to document all side effects reported by either the patients or their treating doctors. For more transparency and in the interest of seriously ill patients, the national authority would publicise a list of approved compassionate use programs on its official website (Sou, 2010; BASG, 2017).

In Austria, Article (83) was implemented into the Austrian legislation by amending the Medicinal Product Act (AMG) in 2009 specifically in § 8a. According to AMG the compassionate use program application can only be submitted by either the manufacturer or a

sponsor of validated clinical trials for the respective medicinal product, or by the applicant of a centralised MA for the respective medicinal product. Moreover, Austria is one of the MSs that legally differentiate between compassionate use programs and named patient use.

Notably, the medicinal products which would be imported to Austria in the context of a temporarily approved CUP are not subject to the preconditions of the Medicinal Products Importation Act (Arzneiwareneinfuhrgesetz 2010).

Frequently **Named Patient Use** is confused with the compassionate use programs or classified to be a variety of it however, the named patient use does not fall within the scope of Article (83) though is regulated in Article (5) of Directive 2001/83/EC.

Named patient use is classified based on authorised health care professional´s intention to treat a named individual patient with serious condition with an unauthorised promising medicine whereby the treating doctor assumes full responsibility for the process and has to contact the manufacturer directly. Many MSs clearly distinguish the compassionate use programs or cohort as termed in some MSs from other terminologies as named patient use or expanded access programs (EMA, 2007, 2010; Sou, 2010).

The regulatory framework, the management and evaluation process of compassionate use programs in Austria are fully detailed in the **'Guideline for Compassionate Use in Austria'** (BASG, 2015, 2017).

Recently, several compassionate use programs were established in association with treatments for COVID-19. A keen interest in compassionate use was expanded as a result of lack of effective treatments or vaccines against the novel virus. In the literature there are several examples of medicinal products which were utilised in CUPs for treatment of severe COVID-19 such as:

- IV infusion of Allogeneic cardiosphere-derived cells (CAP-1002) in **6** COVID-19 patients with Acute respiratory distress syndrome (ARDS) (Singh *et al.*, 2020).
- Subcutaneous injection of Leronlimab (a monoclonal antibody developed to treat HIV infection) in **23** critical COVID-19 patients (Yang *et al.*, 2020).
- **5** COVID-19 patients with severe pneumonia treated with RUCONEST (a recombinant human C1 inhibitor, conestat alfa) (NewsRX LLC, 2020).

- IV administration of remdesivir (viral RNA polymerase inhibitor) to **86** pregnant women with severe COVID-19 (Burwick *et al.*, 2020).
- Treatment of intubated COVID-19 patients with solnatide (a peptide-based drug has proven to be effective in treating lung conditions) (RTDs Group, 2021).

5.4 Rolling Review

Rolling Review is another effective approach designed by EMA, specifically to be used in emergency situations. The ad hoc procedure allows EMA to review the data for an upcoming likely application as soon as they are available. In other words, it allows exceptionally continuous assessment of generated data during the development phases and before the formal submission of a complete dossier for a new MA or for an extension of an existing MA. Consequently, EMA will manage to review the MAA dossier in advance while ensuring robust scientific conclusions.

The decision to conduct a rolling review procedure is based on the EMA emerging health threats plan and starting them involves a specific arrangement by the COVID-ETF since this taskforce is contributed to assessment of the rolling data. As for other procedures, the Rapporteur and Co-rapporteur team manages the rolling review assessment, and the final opinion will be adopted by the CHMP. The evaluation of data is achieved via rolling review cycles whereby the company submits the recent set of data periodically for evaluation. Each cycle regularly takes two weeks, depending on the amount of submitted data.

The CHMP will then decide whether the data package is sufficient to proceed with a formal regulatory procedure. Accordingly, the company will apply for the formal MA or the extension. As an effect of this prospective strategy, the review´s timetable will be significantly shortened depending on the amount of data included in the rolling review cycles (Fig.1).

Lately, all COVID-19 treatments and vaccines, whether they are already authorised or are currently under evaluation are profiting from the rolling review procedure since a robust evidence on quality, safety and efficacy is concurrently assured (GLANVILLE, 2021b, 2021c).

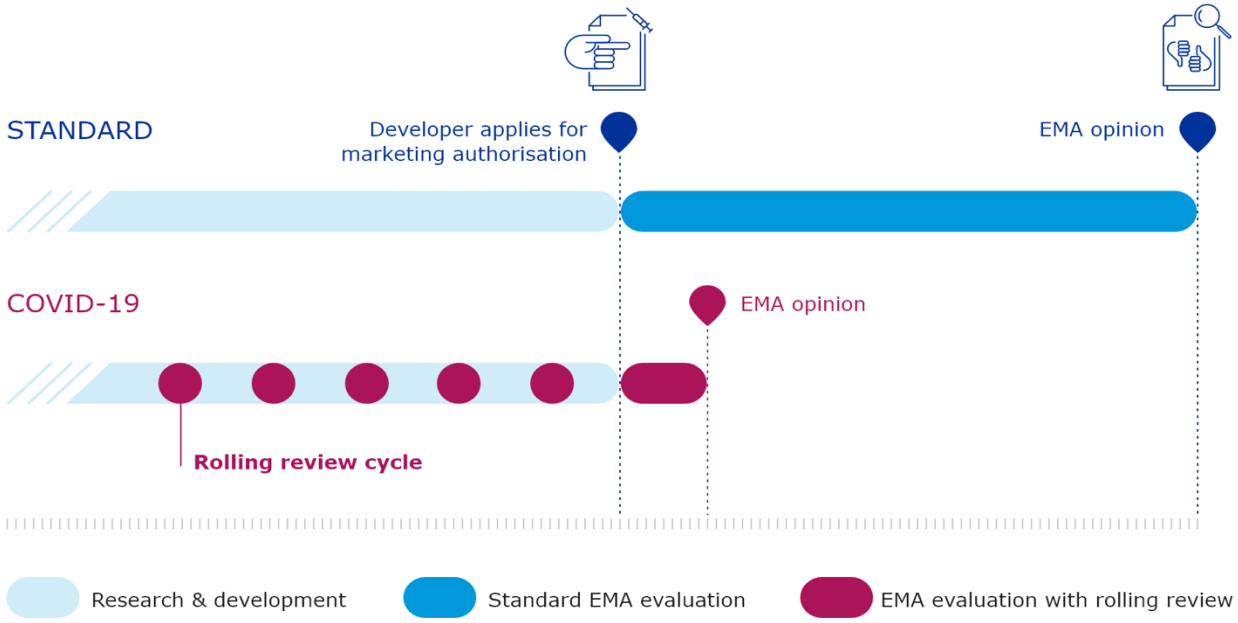

Figure 1: Rolling review cycles prior to the formal marketing authorisation application and their influence in accelerating the evaluation process (GLANVILLE, 2020b)

5.5 Extension of Indication and Extension of marketing authorisation

Pursuant to Variation Regulation (EC) No 1234/2008 amended by Commission Regulation (EU) No 712/2012, variations to a marketing authorisation are classified into categories (Type IA, Type IB, Type II, urgent safety restrictions and extension of marketing authorisation). The classification is based on the level of risk implied to public and the effect of these variations on quality, safety and efficacy of the involved medicinal product. The Variation Regulation Article (2) defines a variation to the terms of a marketing authorisation as: 'any amendment to the information referred to in Article 12(3) to 14 of Directive 2001/82/EC and Annex I thereto, Articles 8(3) to 11 of Directive 2001/83/EC and Annex I'. In addition to other EU legislations related to the term of marketing authorisation for medicinal products for humans. Correspondingly, the Article (2) defines `Major variation of type II' as 'a variation which is not an extension and which may have significant impact on the quality, safety or efficacy of the medicinal product concerned' and 'Extension of marketing authorisation' or extension as 'a variation which is listed in Annex I and fulfils the conditions laid down therein' (Publications Office of the European Union, 2008; Puplications Office of the European Union, 2012).

The extension of a new therapeutic indication or the modification of an existing indication is classified in the Annex II, as major variation of type II. The Marketing Authorisation Holder (MAH) is requested to notify the Agency six months in advance of their intention to apply for an extension of indication. The application should include all elements listed in Annex IV of the Variations Regulation. The submission of such applications follows a monthly definite date while their evaluation follows a 90-day timetable. Moreover, the CHMP leads the assessment and adopts the final opinion for the extension of indication.
A Commission Decision of amendment shall be granted within 2 months (EMA, 2021d).
Regularly, a new indication falls within one of the following criteria:

- 'a new target disease'
- 'different stages or severity of a disease'
- 'an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors'
- "change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination"
- 'change from treatment to prevention or diagnosis of a disease'
- 'change from treatment to prevention of progression of a disease or to prevention of relapses of a disease'
- 'change from short-term treatment to long-term maintenance therapy in chronic disease' (EC, 2007).

Conversely, in a couple of cases a type II variation procedure cannot be applied to extend an indication, instead a separate application or extension of marketing authorisation could be acceptable, for example:

- Extension of non-orphan therapeutic indication of an orphan authorised medicinal product. In general, it is not acceptable to group an orphan and a non-orphan indication within the same marketing authorisation. Here, a separate application for the new non orphan indication may be considered.

- Addition of a new therapeutic indication based on less comprehensive data to an authorised medicinal product. In case the medicinal product was already granted a standard marketing authorisation, a standard data requirement for the new indication within the same marketing authorisation shall apply. Alternatively, a separate marketing authorisation (conditional or under exceptional circumstances) may be submitted. If the medicinal product has been already authorised conditionally or under exceptional circumstances, an extension of indications (under certain obligations) is possible.
- Grouping of an extension of indication and an extension of marketing authorisation. In this case, an extension of marketing authorisation procedure and its standard timetable (210 days) is applicable (EMA, 2021d).

Extension of marketing authorisation is also regulated in the Variation Regulation and is applicable whenever the intended variation is considered to substantially change the terms of this marketing authorisation. Such variations cannot be handled using variation procedure. These fundamental changes which impose an extension of marketing authorisation are listed in Annex I (EMA, 2018g). The Annex I involves three main categories of changes (in which two categories are related to human medicinal products):

1- 'Changes to the active substance(s)'
2- 'Changes to strength, pharmaceutical form and route of administration'(EC, 2019)

Usually, Extension applications are associated with a considerable amount of data, particularly when coupled with either extension of new indication or modification to an existing one. Due to organisational reasons, the MAH is requested to send a 6 months' notice in advance of their intention to apply for an extension to EMA. The Extension application will then be submitted by the MAH according to submission deadlines detailed in specific timetable available on EMA´s website. Given that, the assessment of such applications follows the exact same procedures as for granting the related initial marketing authorisation, the CHMP will adopt an opinion in accordance with a standard timetable which normally takes 210 days. After a positive opinion, the Commission shall grant an Extension for the marketing authorisation (within 67 days from CHMP´s opinion). The Extension can be granted as a new marketing authorisation or can be included in the initial marketing authorisation.

Another key point which is highlighted in the Variation Regulation is variations concerning human influenza vaccines. The changes to active substance of human influenza vaccine due to seasonal, pre-pandemic or pandemic situation will not be handled as Extension. In case an influenza pandemic is recognised by WHO or by the European Community, the Article (21) states clearly that:

"the Commission may exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human influenza vaccine, where certain non-clinical or clinical data are missing". Where the missing data will be submitted by the MAH according to an agreed timeframe (Publications Office of the European Union, 2008, 2013; EC, 2019; EMA, 2021d).

More details on the different categories of variations, procedural guidance, the required documentations and related Annexes are provided by EC (Variations Guidelines) and EMA in the following guidance:

- **Variations Guidelines: "Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, II a, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures"**
- **'European Medicines Agency post-authorisation procedural advice for users of the centralised procedure'**
- **'Guidance on the categorisation of Extension Applications (EA) versus Variations Applications (V)'**
- **'Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure'**

After all, EMA is ready to apply further flexibility and even shorten the review times for applications for extension of indications or Extension of authorised medicinal products which are potentially effective against COVID-19. MAH of authorised products which can be repurposed to treat or prevent COVID-19 are encouraged to contact and share their plans with the Agency (EMA, 2020d, 2020c).

5.6 Other considerations and rapid procedures

5.6.1 Rapid scientific advice

Rapid scientific advice is an exclusive scientific advice procedure, designed to facilitate the prospective planning for development of treatments and vaccines for COVID-19 while the general principles of the standard scientific advice remain unchanged.

In general, scientific advice is not a pre-evaluation of the submitted data but rather a support of development strategies and evidence generation planning. However, they are not legally binding. Scientific advice is laid down in Article 57-1 (n) of Regulation (EC) No 726/2004 as one of the tasks assigned to EMA.

A rapid scientific advice comprehends the following features:

- Flexibility is considered in regard to 'type and extent of the briefing dossier, which need to be discussed on a case-by-case basis'
- The scientific advice regular fees are reduced by 100% on the basis of EMA Executive Director decision (EMA, 2020b).
- Pre-specified submission deadlines do not apply on submission dossiers concerning COVID-19 treatments and vaccines.
- Reduction of total review time to 20 days instead of regularly 40/70 days. This is accomplished through the expedition of all significant stages of the process including validation, assessment report communication, peer review and adoption.

Developers who intend to seek a rapid scientific advice should contact the Agency electronically to check the suitability and maturity of their request for the rapid scientific advice procedure. Once the request is verified, the accelerated workflow for scientific advice starts. In case of an immature development plan, EMA and the COVID-ETF will provide an early guidance and support instead. The process principally involves the Scientific Advice Working Party (SAWP) along with additional expertise of the COVID-ETF whereas the advice is adopted by the CHMP.

'**The European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance'** provides the medicine´s developers with all related procedures step

by step, SAWP requirements and further useful information about scientific advice. (EMA, 2020a, 2020c).

5.6.2 'Rapid agreement of a paediatric investigation plan and rapid compliance check'

The review of application for a Paediatric Investigation Plan (PIP), deferral or waiver [1]in context of COVID-19 treatments and vaccines shall be prioritised and accelerated, by which legislative requirements are applicable. Compliance checks will be as well expedited.
Seeing that, the scientific outcomes of such applications should remain robust, an accelerated and flexible strategy will be individually decided. The Paediatric Committee (PDCO) together with scientific support from COVID-ETF are responsible for the evaluation of the applications for rapid PIPs.
A PIP is a development plan for the necessary data that support the authorisation of medicines for children. The PIP is regulated in EU Paediatric Regulation, (EC) No 1901/2006 and must be approved by the PDCO in advance (European Parliment, 2006).
Moreover, it includes details of the paediatric studies and agreed timelines. The results of these studies should be included in the application`s dossier for each new medicinal product unless the medicine was granted a PIP deferral or waiver.

Compliance check is a confirmation of full or partial completeness of measures and studies which are agreed to in a PIP. A full compliance check is assessed by the PDCO which in turn adopts a final opinion.
A rapid PIP and compliance checks introduce the following advantages:

- Pre-specified submission deadlines do not apply on submission dossiers concerning COVID-19 treatments and vaccines for children.
- Developers may provide a focused scientific documentation, which will be discussed on a case-by-case basis.

[1] PIP deferral is a measure that allow an applicant for MAA to defer the development procedures concerning children until, for instance, the medicine proves to be effective and safe in adults. While Waiver is referred to medicines which are only suitable for adults and there is no need to investigate them for pediatrics.

- Reduction of total review time for a PIP to a minimum of 20 days instead of normally up to 120 days review time. This is accomplished through the expedition of all significant stages of the process including validation, assessment report communication, peer review and adoption.
- The timeframes for a compliance check prior to a MAA will be determined in proportion to urgency and can be shortened to 4 days if necessary.
- Simultaneous submission of PIP to international regulators (e.g., FDA) to encourage global exchange.

Sponsors of potential COVID-19 treatments and vaccines are strongly advised in early stages of development to consider the paediatric requirements and to communicate with the Agency as soon as possible. Actually, a pre-submission interaction with EMA is highly recommended in order to avoid any delays (EMA, 2014, 2020c).

5.6.3 PRIority MEdicines (PRIME)

According to EMA, "PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier"(2018f).

The PRIME scheme creates opportunities for early recognition of products which are likely eligible to an accelerated procedure, hence allow advanced regulatory support und scientific fostering of such products through their development stages and ensure that, the generated data meet the MAA requirements. The scheme targets mainly medicinal products with innovative therapeutic indications. In other words, medicinal products that fulfil the accelerated assessment criteria.

The applicants of medicines with major therapeutic advantage to patients, can submit a PRIME eligibility request to EMA which will be reviewed by the SAWP before the final adoption within 40 days by the CHMP. Applying for PRIME is usually done based on preliminary

evidence from clinical phase that the medicinal product under investigation meets to a significant extent an unmet medical need, which is called proof of concept.
Data on medicinal products which are eligible to the PRIME scheme based on preclinical or very early clinical data is called proof of principle (CHMP, 2018; EMA, 2018d).
Once a medicinal product accesses the PRIME scheme, applicants gain the following benefits:

- Appointment of a rapporteur from the CHMP or the Committee on Advance Therapies (CAT) to give continuous support and guidance to manage a successful MAA.
- Organisation of a kick-off meeting with the CHMP/CAT rapporteur besides a multidisciplinary group of experts in order to provide advice on the overall development plan as well as recommended regulatory strategy.
- EMA addresses a contact point who will coordinate the arrangements offered through the scheme.
- Scientific advice at critical development milestones, which may involve consultation from additional stakeholders as for example 'health technology assessment (HTA) bodies and patients'
- A confirmation of eligibility of the medicine for accelerated assessment by the time of application for MA (EMA, 2018f).

The scope of the PRIME scheme, its features, eligibility criteria and an overview of the related procedure are all included in EMA guidance:

- **'Enhanced early dialogue to facilitate accelerated assessment of Priority Medicines (PRIME)'**
- **'European Medicines Agency Guidance for applicants seeking access to PRIME scheme'**

In the context of COVID-19 treatments and vaccines, the scheme can be a great support for the applicants mainly in the early stages of development.

Overall, EMA in cooperation with other regulatory authorities in the EU are fully committed to support, by all means, the development and marketing authorisation of COVID-19 treatments and vaccines. The Agency has arranged several measures to facilitate the delivery of successful applications which save time and shorten the review timeframes.

6 COVID-19 treatments and vaccines in the EU

This chapter discusses the COVID-19 treatments and vaccines in the EU whether already authorised or recommended under Article 5(3) by EMA until the end of February 2021.

The global spread of the SARS-COV2 has intensely encouraged an international augmentation in regard to research and development of effective and safe treatments and vaccines (Chitalia and Munawar, 2020). Nevertheless, this scientific expansion was roughly challenged by the fact that development of safe, efficacious and high-quality medicines and vaccines is regularly time intensive.

Under such circumstances and due to the urgent situation, scientific and clinical communities along with health authorities are directing their focus alternatively, in one hand, on the repurposing of either under investigation or authorised drugs and vaccines. On the other hand, on establishing multi-centre large scale clinical trials and thus enhancing the robustness of the generated data.

Through the repurposing concept, scientists are able to gain insights for COVID-19 therapeutics and vaccines based on demonstrated similarity between SARS-COV2 and other viruses like MERS-COV, SARS-COV or HIV (Kliger and Levanon, 2003; Lu *et al.*, 2020).Thanks to the use of already established technologies and platforms for these viral infectious diseases, medicines and vaccines developers have, by all means, accelerated the detection and development of therapeutic and prophylactic solutions against COVID-19.

This approach involves repurposing of, for example, antivirals, monoclonal antibodies, immune modulators and vaccines (Ahmed, Quadeer and McKay, 2020; Florindo *et al.*, 2020). According to this concept a significant number of therapeutics and vaccines were considered, tested and thereupon, have undergone clinical trials, for example:

- **Hydroxychloroquine/ Chloroquine**: antimalarial drugs, some recent evidence has suggested they have anti-SARS-COV-2 activity in vitro. However, the trials on both medicinal products were discontinued due to the lack of proof of efficacy and reported cardiotoxicity (Chaplin, 2020; Ortolani and Pastorello, 2020).

- **Lopinavir-ritonavir**: a combination of the two antivirals for treatment of HIV, was believed to have effect against COVID-19, following demonstrated activity in vitro. Also, the clinical trials on this combination were discontinued due to insignificant therapeutic value (Chaplin, 2020; Magro, 2020).
- **Corticosteroids** which demonstrated clinical efficacy in severe COVID-19 cases (Horby *et al.*, 2020).
- **Remdesivir** has proven earlier to be effective against coronaviruses. The clinical trials have confirmed its efficacy in hospitalised patients suffering pneumonia and require supplemental oxygen (Sheahan *et al.*, 2017; Chaplin, 2020).
- **Tocilizumab** is an immunosuppressive drug used to treat rheumatoid arthritis. It was tested for its anti-inflammatory activity on COVID-19 patients. The RECOVERY study has concluded that tocilizumab reduces the mortality of hospitalised patients with severe COVID-19, shortens their discharge time and alleviate their need for mechanical ventilation (University of OXFORD, 2021).

By the end of February 2021, a total of one medicine and three vaccines were authorised EU-wide in addition to two COVID-19 treatments recommended under Article 5(3). Correspondingly, two treatments (monoclonal antibody regdanvimab, REGN-COV2) and three vaccines (CVnCOV, NVX-CoV2373, COVID-19 Vaccine Janssen) were under evaluation by the EMA (GLANVILLE, 2021b, 2021c). In addition to 'an EU programme of COVID-19 convalescent plasma collection and transfusion' which was endorsed by the EC and the competent authorities for blood and blood components in each Member State (EC, 2020c).

6.1 COVID-19 treatments authorised in the EU

6.1.1 Remdesivir (Veklury)

Remdesivir was one of a series of compounds under investigation for antiviral activity. These molecules have shown an inhibitory activity against a number of RNA viruses such as Hepatitis C, Influenza A and SARS-COV.

The antiviral activity is attributed to competitive inhibition of viral RNA-dependent RNA polymerase interrupting with the replication of viral RNA. Remdesivir is a designed prodrug which should be intracellularly converted into the active form that interferes with the viral RNA synthesis (Fig. 2)(Cho *et al.*, 2012).

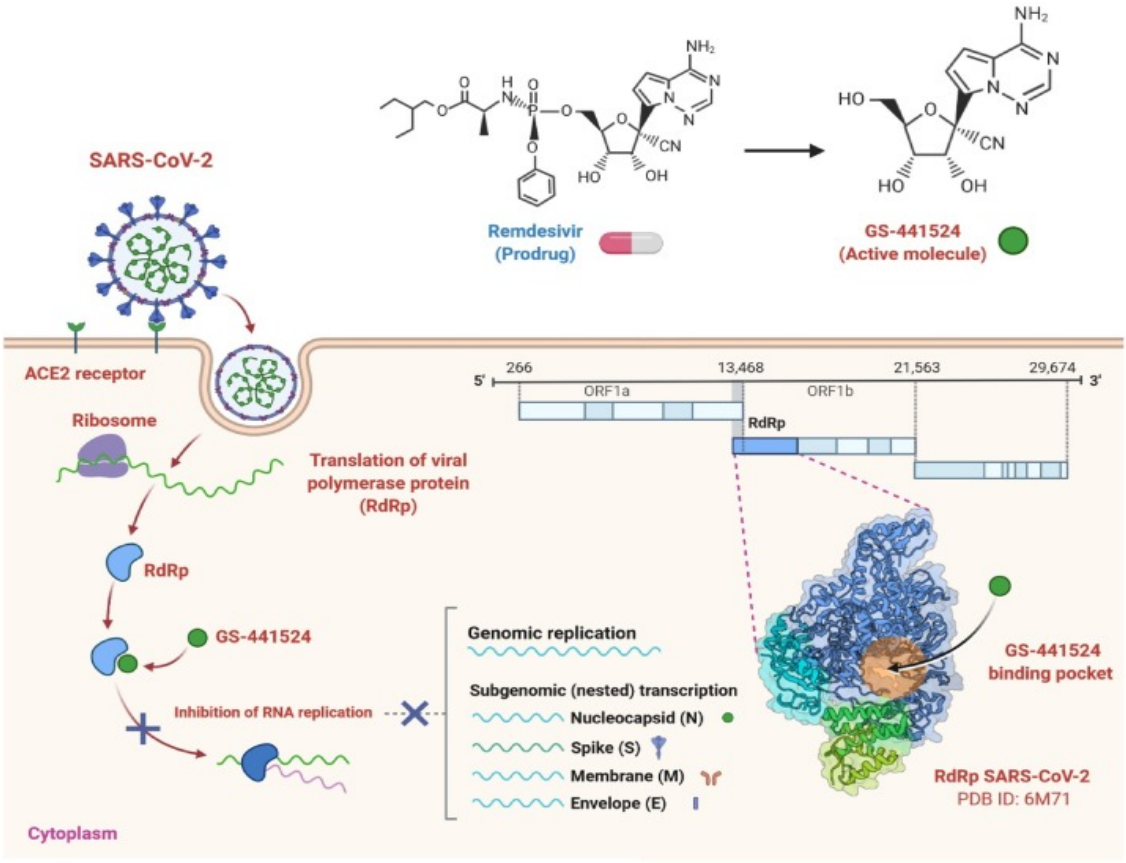

Figure 2. The possible mechanism of action of remdesivir against coronavirus. It also indicates the 3D structure of the binding site of remdesivir on SARAS-COV 2(on right side) (*Awadasseid* et al., *2021)*

The broad-spectrum antiviral was initially tested in clinical trials based on in-vitro and pre-clinical potency against Ebola virus. The results of the trials have revealed that remdesivir treatment was ineffective in comparison with other treatments however, it have given an initial indication about its safety profile (Mulangu *et al.*, 2019).

As SARS-COV2 emerged, Remdesivir was one of the most promising candidates to undergo clinical trials due to its well-established antiviral activity against coronaviruses including SARS-COV and MERS-COV in preclinical studies. Thereupon, a number of clinical trials were conducted to test Remdesivir´s safety and efficacy against COVID-19. The outcomes of these studies were encouraging in which remdesivir was contributed to clinical improvement of hospitalised patients with severe pneumonia as well as to reduction in recovery time. The safety profile of remdesivir across all studies was acceptable (Beigel *et al.*, 2020; Richardson, Bhagani and Pollara, 2020; Saint-Raymond *et al.*, 2020; Wang *et al.*, 2020).

Furthermore, remdesivir was used in compassionate use programs which was supported by the recommendations of EMA (FRANCISCO, 2020; Grein *et al.*, 2020).

On 30 April 2020, EMA has started a rolling review of remdesivir for the treatment of COVID-19. The CHMP´s decision was based on the preliminary results of the National Institute of Allergy and Infectious Diseases (NIH) clinical trial, which has proven accelerated recovery in advanced COVID-19 patients who have received remdesivir (CZARSKA-THORLEY, 2020e; NIH, 2020).

On 8 June 2020, EMA has received the official application for conditional marketing authorisation for remdesivir and has started the assessment of the first treatment for COVID-19 (CZARSKA-THORLEY, 2020c). Forthwith, the CHMP has given a positive opinion for Veklury and has recommended its approval in the EU. Accordingly, the EC has authorised conditionally Veklury for 'the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen' (HRABOVSZKI, 2020b).

On 15 October 2020, WHO has updated its recommendation status on remdesivir based on the interim results of the SOLIDARITY Trial which has found that remdesivir 'had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients' (Consortium *et al.*, 2020).
According to WHO, the certainty of the data yet based on the meta-analysis is considered low and more research and enrolment in trials testing remdesivir should definitely continue. In response to WHO´s proposition, EMA has stated that:
'the WHO recommendation is conditional and based on a systematic review and network meta-analysis of four randomised trials'.
EMA has advised health care professionals to follow the authorised product´s information as well as updated national treatment´s guidelines when using remdesivir. Additionally, the Agency has requested to review the full SOLIDARITY data, along with other relevant data, to verify the need to recondition the marketing authorisation of remdesivir in the EU (PINHO, 2020e).

Despite the clinical benefits of remdesivir, its use is limited due to its intravenous administration and contraindication in patients with renal impairment or elevated liver enzymes (5 times above normal range) (Richardson, Bhagani and Pollara, 2020).
Overall, further investigations, observational studies and clinical trials involving remdesivir are contemporarily ongoing.

EMA has actively updated and published all information and guidance related to remdesivir such as:

- **'Summary on compassionate use for Remdesivir Gilead'**
- **'EMA recommends expanding remdesivir compassionate use to patients not on mechanical ventilation'**
- **'Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan'**
- **'Veklury: EPAR- public assessment report'** and **'EPAR-Assessment report- variation'**

6.2 COVID-19 treatments adopted under Article 5(3)

Pursuant to Article 5(3) of Regulation (EC) No 726/2004, the Executive Director of the EMA, the Executive Director of the EC or a Member State may request the CHMP for a scientific opinion on the use of specific medicines. This procedure is classified under Referrals by which an individual medicine or class of medicines is referred to EMA for scientific assessment aiming to support the national decisions and to provide a harmonised opinion across the EU (EMA, 2018h; CZARSKA-THORLEY, 2020a)

6.2.1 Dexamethasone

Dexamethasone is a synthetic steroid hormone which belongs to the corticosteroids class. It is a potent anti-inflammatory immunosuppressive agent which is indicated to treat a wide range of diseases and symptoms such as allergic conditions, asthma in addition to ophthalmic, oedematous and respiratory conditions (National Center for Biotechnology Information, 2021).

Dexamethasone has efficacious inhibitory effect on pro-inflammatory factors such as cytokines (interleukin IL-1, IL-2, IL-6), TNF and prostaglandins which are responsible for vasodilation and leukocyte stimulation. Dexamethasone has also many immunomodulating effects by interfering with the specialised activities of immune cells such as T cells and B cells.

In severe COVID cases, the progressed viral infection causes a serious damage to lungs (ARDS) resulting in severe inflammation (cytokine storm), further lung injury and interstitial oedema. By such complications, the use of dexamethasone has demonstrated to be exclusively beneficial as a result of controlling the immune mediated damage and the inhibition of the hyperinflammatory state in the lungs (Mitre-Aguilar, Cabrera-Quintero and Zentella-Dehesa, 2015; Ahmed and Hassan, 2020; Cain and Cidlowski, 2020).

From the beginning, the use of corticosteroid treatment for COVID patients was quite controversial. On one hand, many have recommended its use to mitigate the severe inflammation and the cytokine storm associated with severe pneumonia (a serious complication of coronavirus infection) based on reliable clinical observations (Shang *et al.*, 2020). On the other hand, clinical evidence from previous studies on SARS-COV and MERS-COV patients has not favoured its systemic indication for COVID-19 cases.

This conclusion may be referred to first, corticosteroid's immunosuppressant effect, inhibiting an immune response against the virus. Second, the delayed viral clearance and third, the relatively serious adverse effects of corticosteroids therapy such as diabetes, osteoporosis and secondary bacterial or fungal infections (Lee *et al.*, 2004; Xiao *et al.*, 2004; Arabi *et al.*, 2017; Russell, Millar and Baillie, 2020).

In the light of this ongoing debate and upon the meta-analysis of data from the RECOVERY trial, WHO has updated its guidance **'corticosteroids for COVID-19'** to include two recommendations:

- "We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with **severe and critical COVID-19** (strong recommendation, based on moderate certainty evidence)". This recommendation applies to the use of low dose of corticosteroids for a short duration whereby the suggested dose 'is 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours for 7 to 10 days'.
- "We suggest not to use corticosteroids in the treatment of patients with **non-severe COVID-19** (conditional recommendation, based on low certainty evidence)" (WHO, 2020a)

On 18 September 2020, EMA has approved the use of dexamethasone in hospitalised COVID-19 patients who require oxygen support. The use of dexamethasone was recommended for 'adults and adolescents (from 12 years and weighing at least 40 Kg)' to be given either orally, as intravenous injection or infusion (CZARSKA-THORLEY, 2020a).

The use of dexamethasone was reviewed under Article 5(3), upon a request from the Agency´s Executive Director for a scientific opinion on 'potential clinical use of dexamethasone in the treatment of hospitalised adult patients with COVID-19, for oral and intravenous medicinal products'. The Agency´s decision was supported by the thorough evaluation of the results from the RECOVERY clinical trial. The study has concluded that:

"In patients hospitalised with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomisation but not among those receiving no respiratory support".

Furthermore, the study has shown that the use of dexamethasone was associated with lower risk of mechanical ventilation in patients who were receiving oxygen and shorter duration of hospitalisation (Horby *et al.*, 2020, 2020).

The dose of dexamethasone used in the RECOVERY trial was '6 mg per day for up to 10 days' which is reasonably a low-dose therapy. By 6 mg per day, the patients will suffer manageable side effects such as hypertension, diabetes, osteoporosis and weight gain and they will unlikely develop a glucocorticoid resistance. As mentioned in the preliminary report,

four cases of serious adverse events were reported and deemed to be related to dexamethasone, by which all of them are known side effects of glucocorticoids namely hyperglycaemia, gastrointestinal haemorrhage and psychosis (Cain and Cidlowski, 2020; Horby *et al.*, 2020).

Owing to the facts that dexamethasone is low in cost, easy to administer and readily available worldwide, gave its recommendation a further strength (WHO, 2020a).
Information on the procedure, the scientific discussion and the CHMP´s opinion on Dexamethasone for COVID-19 patients is detailed in the assessment report published of the EMA homepage: **'Dexamethasone- COVID-19- Article-5(3) procedure: Assessment report'**

6.2.2 REGN-COV2 (casirivimab and imdevimab)

REGN-COV2 is a combination of novel noncompeting humanised monoclonal antibodies namely casirivimab and imdevimab. A recent study has strongly suggested that combined therapies in context of neutralising antibodies can notably diminish the mutational escape by SARS-COV2. Accordingly, the two antibodies were chosen to potentially bind to specific and non-overlapping sites of the viral target since the simultaneous mutations at two concrete genetic sites are unlikely to emerge (Baum *et al.*, 2020).

Casirivimab and imdevimab combination target the receptor binding domain (RBD) of the SARS-COV2 spike protein, by binding effectively to different, non-overlapping epitopes of the spike protein, and thus block the viral attachment and entry into human cells through

Angiotensin-converting enzyme 2 (ACE2) receptors (Fig. 3)(Weinreich *et al.*, 2020; Deb, Molla and Saif-Ur-Rahman, 2021).

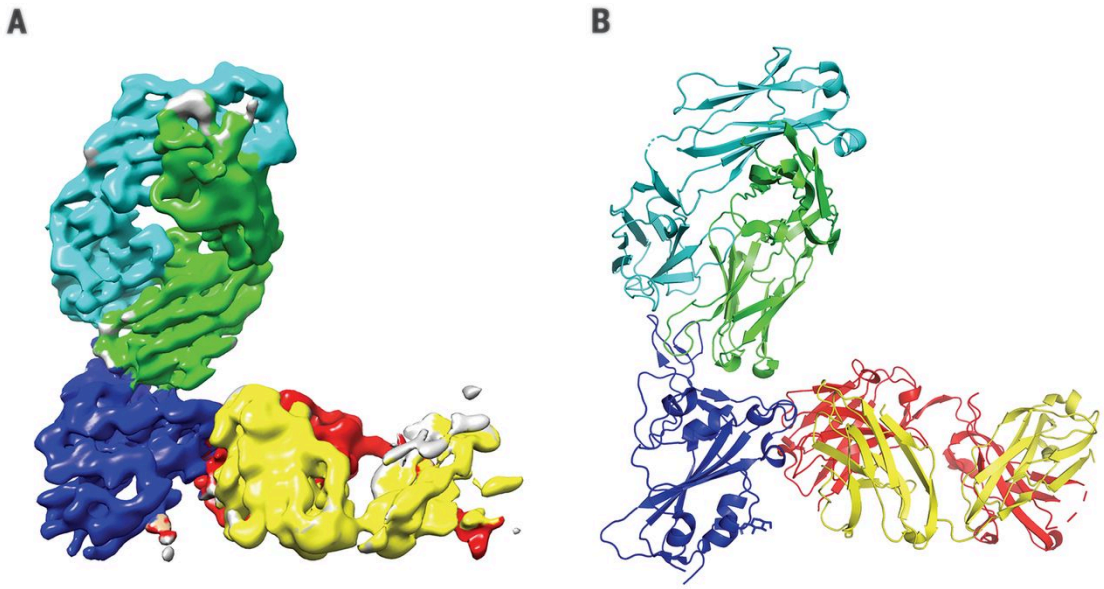

Figure 3 Complex of REGN-COV2 with the RBD of SARS-COV2 spike protein. RBD is dark blue, REGN10933 (Casirivimab) Fab fragment heavy and light chains are green and cyan, respectively and REGN10987 (Imdevimab) Fab fragment heavy and light chains are yellow and red, respectively (Hansen et al.*, 2020)*

On 26 February 2021, the CHMP has finalised a scientific opinion concerning the use of casirivimab and imdevimab to treat COVID-19 patients. The antibodies combination is yet not authorised in the EU by the end of February 2021 but the Agency´s recommendations aim to support and harmonise the national administration of the REGN-COV2in the EU.
EMA advice was issued based on the assessment of available quality data and an ongoing clinical trial investigating the two antibodies (CZARSKA-THORLEY, 2021b).
The planned phase 1-3 trial has shown in its interim analysis that “the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group”.
The study has also shown that patients, whose own immune systems have not yet responded to the virus, in particular non-hospitalised patients would benefit far more from this treatment, while those who are hospitalised or already developed an immune

response have shown no additional improvement or even may suffer worse clinical outcomes (Weinreich *et al.*, 2020).

According to EMA´s recommendation, the combined antibodies may be indicated "for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID and who are at high risk of progressing to severe COVID-19" whereby the recommended dose is '1200 mg of casirivimab and 1200 mg of imdevimab administered as single intravenous infusion' (EMA, 2021e).

The recommendations and the conditions of the use of casirivimab and imdevimab are fully detailed in the EMA guidance:

'**REGN-COV2 antibody combination (casirivimab/imdevimab) COVID-19 Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring'**

Parallel to the EMA´s advice, the rolling review of the combined therapy is ongoing until sufficient amount of data is available to apply for a marketing authorisation (CZARSKA-THORLEY, 2021b).

6.3 COVID-19 Vaccines authorised in the EU

Regularly, vaccine development is a long and complex process which is progressed in sequential steps. With the intention of mitigating the COVID-19 pandemic, not only the vaccine development process has been accelerated, but also its evaluation for marketing authorisation. Yet, the regulatory standards of safety, quality and efficacy have to be fulfilled as usual to approve such vaccines in the EU.

To achieve swift development and authorisation of COVID-19 vaccines, many efforts and resources were allocated for that purpose, for example:

- Both, companies and public health authorities, have specified massive financial and human resources to support rapid development of vaccines.
- Combining of different clinical trial phases or running some studies simultaneously, when possible.

- Using the same developing techniques (i.e., platform technologies) and existing facilities as for other vaccines.
- Companies are expanding in advance their manufacturing capacity in proportion to the necessary large-scale production.
- Designing new development approaches that can boost the capacity of production.
- Regulatory authorities are redirecting resources to facilitate processes and expedite the evaluation and approval of COVID-19 vaccines (rapid scientific advice, rolling review, etc.)
- Additional monitoring and special pharmacovigilance plan for COVID-19 vaccines (EC, 2020d; GLANVILLE, 2020a).

As exceptional measures of transparency concerning regulatory activities for COVID-19 treatments and vaccines, EMA is regularly publishing all the available data and updates on each authorised vaccine in more expedited manner as usual. By which some of this information is normally not publicly shared. This includes European Public Assessment Reports (EPAR) which provide details on product information, medicine overview, full body of the Risk management plan. EMA also publishes on its website monthly COVID-19 vaccine safety updates, the authorised presentations in the EU and the summary of the CHMP´s positive opinion for each approved vaccine (PINHO, 2020d).

6.3.1 Comirnaty (COVID-19 mRNA vaccine)

Comirnaty, also known as Tozinameran (International Non-proprietary Name) or vaccine BNT162b2, is the first authorised vaccine against COVID-19 in the EU.
On 21 December 2020 the European Commission has approved a conditional marketing authorisation for Comirnaty following the recommendation of the vaccine by CHMP. The vaccine was as well granted an approval (either standard or emergency use) in more than 35 countries other than EU and was validated for emergency use by the WHO (PINHO, 2020b; Zimmer, Corum and Wee, 2021).

The global approval of Comirnaty was based on reliable data on vaccine's safety, efficacy and quality in addition to a positive risk-benefit ratio.

The international multicentre phase 2/3 clinical trials have found that “a two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines”.
The trial has investigated the safety and efficacy of two doses of vaccine (30 μg) which were administered intramuscularly with a 21-day interval between them. The reported safety profile was favourable and has included short term and mild to moderate symptoms as pain, redness or swelling at the injection area, fatigue, headache and fever in addition to more severe adverse events as lymphadenopathy and severe allergic reactions. Moreover, the study has assessed the efficacy of BNT162b2 by subgroup (age, race, body mass index, ethnicity and comorbidities associated with higher risk of COVID-19 complications). For all subgroups the vaccine has demonstrated to be efficacious (Polack *et al.*, 2020).

BNT162b2 is an mRNA-based vaccine, an innovative approach which was developed over years in the laboratories, has yet not been exploited in the pharma field until the Covid-19 pandemic. The development of such vaccines, with sufficient resources, is in short time achievable, since the development of RNA-based vaccines requires only the viral genetic sequence in order to be initiated, this technique seemed to meet the urgent and enormous need for a vaccine against COVID-19 (Polack *et al.*, 2020)**.**

A partnership between Pfizer and BioNTech has adopted the mRNA vaccine approach, where the outcomes of the candidate BNT162b2 was impressively promising.

The BNT162b2 encodes the ‘full length SARS-COV2 Spike protein stabilised in the prefusion conformation’ (Sahin *et al.*, 2020; Walsh *et al.*, 2020).
The spike (S) protein in SARS-COV2 acts as binding site to invade human cells through ACE2 receptors. Furthermore, the spike protein triggers human immune response and is the main target of the neutralising antibodies (Padda and Parmar, 2021; Xia, 2021).

The BNT162b2, as a nucleoside modified mRNA, encapsulated in a lipid nanoparticle (LNP) which mediates its in-vivo delivery, has demonstrated to be successfully delivered into

human cells resulting in sufficient SARS-COV2 antigen production and potent induction of SARS-COV2 neutralising antibodies in addition to activation of T cells (Pardi *et al.*, 2018; Sahin *et al.*, 2020).

After intramuscular injection, the encapsulated mRNA is taken up by the cells where the mRNA is released and translated into the SARS-COV2 antigen (S). The peptides, resulting from the intracellular degradation of the spike protein trigger the immune response against the virus (Fig.4) (World Health Organization, 2020).

The level of immunisation was immense, with S-binding IgG concentrations exceeding those detected in COVID-19 human convalescent plasma panel (Sahin *et al.*, 2020).

Although, Comirnaty being the first authorised human RNA-based vaccine, is presenting a powerful tool and a promising concept, several challenges and obstacles need to be further investigated and explained for example:

- The vaccine should be stored at extremely low temperatures (-90°C to -60°C) and once reconstituted can be stored at 2°C to 8°C for up to 5 days. This storage conditions are essential to stabilise the vaccine. Notably, studies are ongoing on stability and formulation optimisation of the vaccine to improve the storage and shipping requirements. Indeed, Pfizer and BioNTech have on 19 February 2021 announced that they managed to keep the vaccine stable at -25°C to -15°C (Polack *et al.*, 2020; Zimmer, Corum and Wee, 2021).
- The vaccine is not recommended, due to lack of data, to pregnant women, immunocompromised persons and children under age 16 (WHO/Europe, 2021). However, Comirnaty is undergoing currently further studies to investigate its safety and efficacy for pregnant women and for paediatrics.
- Another challenge is the lack of long-term safety and efficacy profiles as well as less common adverse events. For that reason, Comirnaty is subjected in EU to additional monitoring and has to fulfil specific obligations within a determined timeline including the submission of final Clinical Study Report which confirms the efficacy and safety of Comirnaty in the next 2 years (EMA, 2021a).
- The virus new variants and the proof of effective protection against them. In this context, EMA has requested an update of data from COVID-19 vaccine developers

and MAH whether their vaccines provide an adequate level of protection against any new variants (PINHO, 2021c).

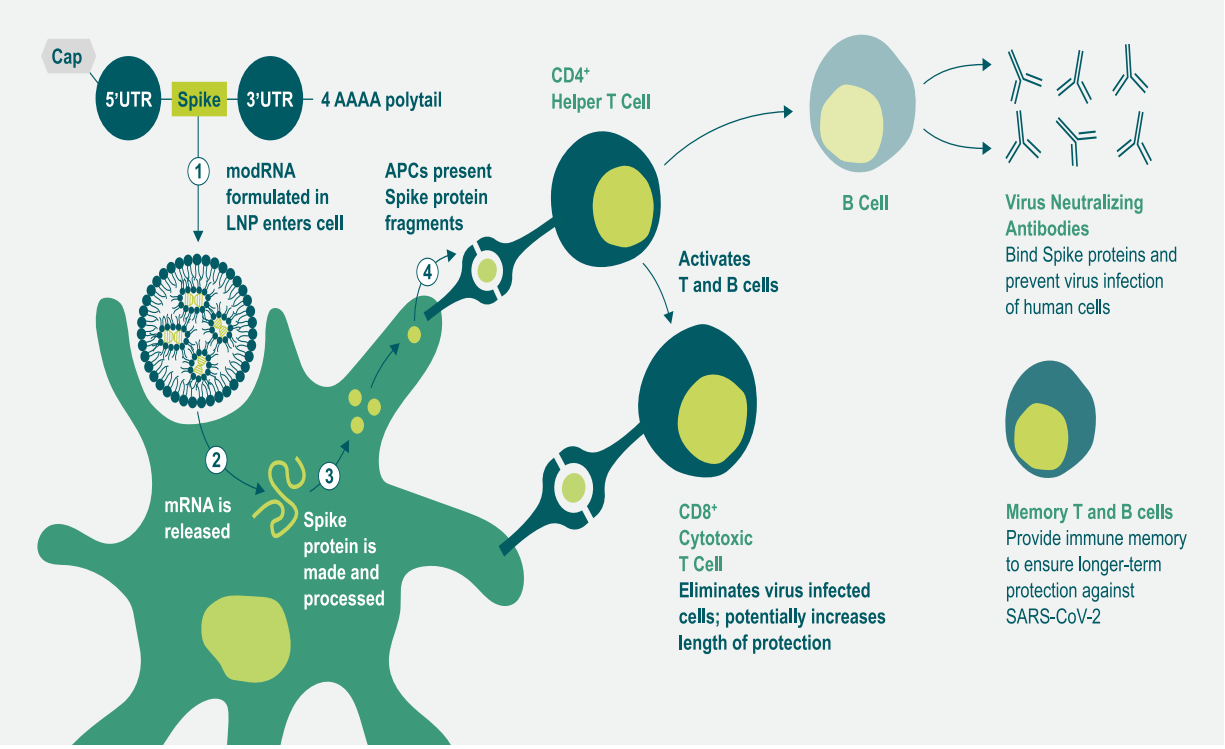

Figure 4 Proposed mechanism of action of mRNA vaccines (BIONTECH, 2020)

6.3.2 mRNA 1273 vaccine (COVID-19 Vaccine Moderna)

On 6 January 2021 the mRNA-1273 vaccine, developed by Moderna and the National Institute of Health (NIH), was granted a conditional marketing authorisation by the EC following the positive opinion of the CHMP 'to prevent Coronavirus disease (COVID-19) in people from 18 years of age', to be the second human mRNA vaccine to be authorised in the EU (GLANVILLE, 2021a).

Similar to BNT162b2, the vaccine is a modified mRNA, encoding the full length of the SARS-COV2 antigen (S), encapsulated in an LNP.

With the same proposed mechanism of action, mRNA 1273 has demonstrated to elicit a significant level of neutralising antibodies even against the new variants B.1.1.7 (from United Kingdom) and B.1.351 (from Republic of South Africa) (Tumban, 2020; Wu, Werner, Koch, *et al.*, 2021; Wu, Werner, Moliva, *et al.*, 2021).

The phase 3 clinical trial investigating the efficacy and safety of mRNA 1273, has concluded that "The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe diseases. Aside from transient local and systemic reactions, no safety concerns were identified". The study has provided evidence of efficacy of mRNA1273 vaccine to prevent symptomatic COVID-19 infection as well as to hinder severe infections. The standard regimen is 2 doses of 100µg mRNA-1273 to be administered by intramuscular injection, 28 days apart.

Most of the reported adverse events were considered mild such as local short-term pain, tenderness and redness at the injection site or delayed injection-site reaction. In addition to moderate systemic adverse events such as fatigue, myalgia and headache.
As mentioned before, the absence of long-term efficacy and safety data and studies on special populations (pregnant women, immunocompromised and children) are the main limitations of mRNA vaccines, therefore further investigations need to be conducted (Baden *et al.*, 2020).

Moderna vaccine can be stored unopened at 2°C to 8°C for up to 30 days and at 8°C to 25°C for up to 12 hours after removal from refrigerator.
Being authorised via conditional marketing authorisation, the MAH of the vaccine needs to fulfil post authorisation conditions and specific regulations including the final Clinical Study Report, confirming the safety and efficacy of the vaccine in 2 years (EMA, 2021c).

6.3.3 Vaxzevria (previously COVID-19 Vaccine AstraZeneca)

A collaboration between the University of Oxford and the British pharmaceutical company AstraZeneca to develop a non-replicating Viral Vector Vaccine, has successfully delivered the COVID-19 Vaccine AstraZeneca to market (Sharma *et al.*, 2020).
The vaccine was granted a conditional marketing authorisation by the EC to prevent COVID-19 in adults, 18 years and older on 29 January 2021, to be the third approved vaccine against COVID-19 across the EU. The decision was based on the recommendation of EMA after the thorough evaluation of data on quality, safety and efficacy of the AstraZeneca vaccine (PINHO, 2021d).

The COVID-19 Vaccine AstraZeneca, known also as ChAdOx1 nCOV-19 vaccine or AZD1222, is designed as a recombinant, replication-deficient chimpanzee adenovirus (CHAdOx1) vector which encodes the full length of the SARS-COV2 Spike protein (S) gene.
After intramuscular injection, the encoded gene will be intracellularly released by the virus and translated into the S glycoprotein which trigger humoral and cellular immune responses (Figure 5)(EMA, 2021b).

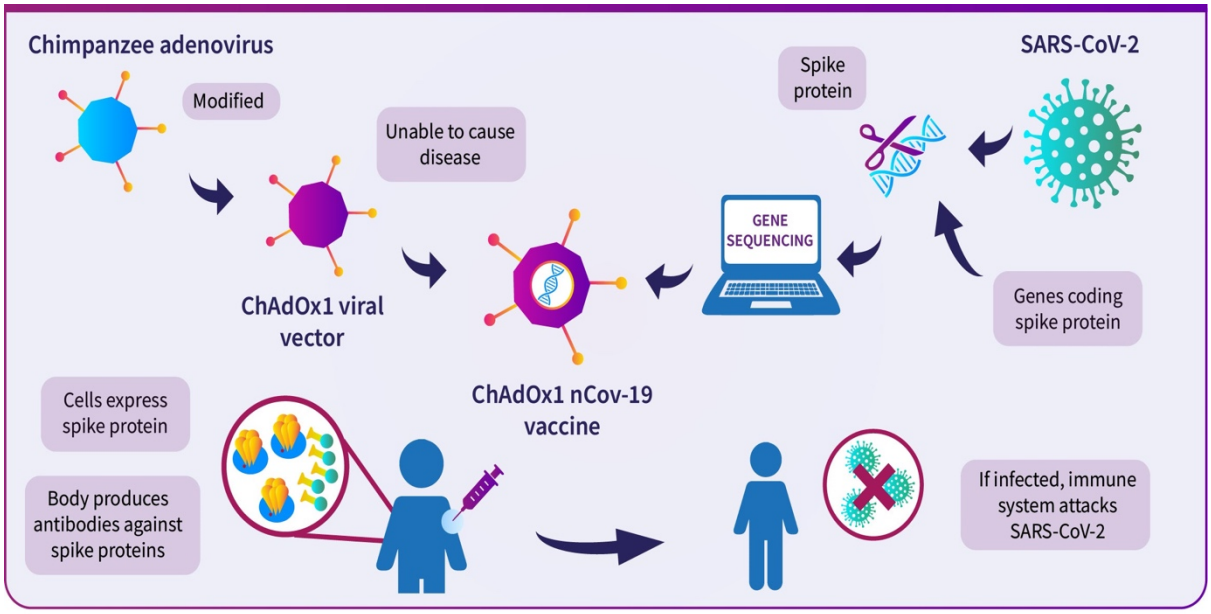

Figure 5 Proposed mechanism of action of COVID-19 Vaccine AstraZeneca (University of OXFORD, 2020)

The results from the ongoing phase 3 clinical trials on ChAdOx1, established in UK, Brazil and South Africa, has shown "in participants who received two standard doses, vaccine efficacy was 62.1% and in participants who received a low dose followed by a standard dose, efficacy was 90.0%" where a standard dose is 5×10^{10} viral particles, administered within an interval of 4 to 12 weeks". Correspondingly, the vaccine has demonstrated significant efficacy to prevent both, symptomatic infection and hospitalisation of COVID-19 in age group 18-55 years. Notably, the older population (Age 56 years and older) was not effectively represented in the trial (12.2%).

The study has also revealed an acceptable safety profile of the vaccine (Voysey *et al.*, 2021). The reported adverse events were mostly mild and short-term including symptoms as local pain, injection site tenderness, headache, fatigue and fever while serious adverse events which may be related to the vaccination included pyrexia and transverse myelitis.

Recently, incidences of thrombosis in brain and abdomen with thrombocytopenia (low platelets count) have been reported in people who received Vaxzevria by which a number of cases were fatal. EMA and its safety committee (PRAC) have reviewed the reported cases and a possible link to the very rare side effect of the vaccine was found. Consequently, the PRAC has advised to list 'unusual blood clots with low platelets as very rare side effects of Vaxzevria' as a very rare adverse event of the vaccine (PINHO, 2021a).

There is evidence supporting that AZD1222 has similar efficacy against the B.1.1.7 variant but the B.1.351 variant seems to be resistant to the vaccine as indicated in a separate study in South Africa (Emary *et al.*, 2021; WHO, 2021a).

As other COVID-19 pandemic vaccines, further studies need to be conducted to maintain the duration of protection and long-term efficacy and safety, particularly in special populations (pregnant women, children, **elderly**, immunocompromised persons).

The AstraZeneca Vaccine is conditionally approved in the EU therefore, the MAH should complete the specific obligations according to the agreed timetable for example submission of the primary analysis and the final clinical study reports of all four clinical trials and conduction of an additional study for elderly and patients with comorbidities, confirming the efficacy and safety of COVID-19 Vaccine AstraZeneca (EMA, 2021b).

Update: COVID-19 Vaccine Janssen:

On 11 March 2021, the COVID-19 Vaccine Janssen was granted a conditional marketing authorisation in the EU. The decision was based on thorough assessment by CHMP of data generated from multicentre clinical trials which has proven the efficacy, safety and quality of COVID-19 Vaccine Janssen in preventing COVID-19 infections in persons from 18 years old.

The concept of this vaccine as well as mechanism of action are similar to those of the AstraZeneca vaccine. The vaccine has demonstrated 67% efficacy with a mild to moderate safety profile (headache, muscle pain, pain at site of injection and nausea), however, unusual blood clots in combination with thrombocytopenia in vaccinated individuals in the United States have also been reported. The investigation of the very rare side effect has been initiated (PINHO, 2021e, 2021b).

6.4 COVID-19 Convalescent Plasma (CCP)

Convalescent plasma is a conventional passive antibody therapy which is known to be effective in treatment of several infectious disease outbreaks. Principally, passive immunisation is more effective as prophylaxis than treatment, however, when used for therapy it is recommended to administer a sufficient level of antibodies, early after the onset of symptoms (Casadevall and Pirofski, 2020).

Plasma collected from recovered COVID-19 patients containing an adequate level of anti-SARS-COV2 antibodies (CCP) is indicated to treat COVID-19 patients.

The use of CCP was supported early as the outbreak was first expanding where no effective treatment was available. Thereafter, an increasing number of studies and randomised controlled trials have investigated the effect of CCP on the clinical outcomes of hospitalised and severe COVID-19 patients. On one hand, several studies have suggested that, convalescent plasma treatment diminishes the SARS-COV2 viral shedding (Zeng *et al.*, 2020), improves the clinical symptoms and mortality in severe COVID-19 patients (Xia *et al.*, 2020), minimises the progression to mechanical ventilation (Avendaño-Solà *et al.*, 2020) and reduces the risk of severe respiratory complications when administered with high titre of antibodies within 3 days after the onset of symptoms (Libster *et al.*, 2021).

On the other hand, more recent evidence proposes that CCP has no significant clinical benefits and does not improve overall mortality in patients with severe COVID-19 (Agarwal *et al.*, 2020; Pathak, 2020; Simonovich *et al.*, 2021).

The RECOVERY trial has also stopped the recruitment to the convalescent plasma arm based on the preliminary analysis of generated data which has shown no significant difference in the 28-day mortality (RECOVERY, 2021).

In view of the current state of knowledge, WHO has advised to use CCP as an experimental therapy or as a starting material for the manufacture of immunoglobulins (WHO, 2021b) while, FDA has revised its Emergency Use Authorisation (EUA) for use of CCP and has approved only 'the use of high titre COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the course of disease' (FDA, 2021). Furthermore, the competent authorities for blood in the EU and the ECDC have agreed that "plasma from recovered patients might be a valuable resource to support the disease treatment within

randomised or case-control trials or observational studies of plasma transfusion and in the development of plasma-derived medicinal products".

The EC has published **'The Guidance document on the collection and transfusion of convalescent COVID-19 plasma'**.

This guidance was first published in April 2020 and was updated twice in the light of the recent findings.

Overall, the effectiveness of CCP should continue to be investigated, ideally through randomised controlled trials where the participants meet predetermined eligibility criteria. It is very important that these trials focus on studying the efficacy of **early** administration of convalescent plasma with **high** SARS-COV2 antibody titres (EC, 2020c).

7 Discussion

With no doubt, the COVID-19 outbreak has been and is still representing a real dilemma for public health authorities in the EU and the whole world especially in managing different regulatory aspects. Where the responsibility to ensure both, the availability of crucial and the approval of safe, effective and high-quality therapies against COVID-19 in relatively short time, reflects a major challenge.

As already acknowledged among the scientific communities, zoonotic infections possess a concerning potentials to spread widely and cause pandemics.

The influenza viruses, for example, have withdrawn significant scientific attention due to their continuous mutations and ability to jump from animals to human.

Recently, corona viruses have as well frequently emerged and caused major public health emergencies. Thereupon the public health authorities worldwide have invested time, experts and resources in preparedness projects and plans as well as research and development of universal antivirals, antibacterials and vaccines to mitigate future infectious disease outbreaks.

The regulatory authorities in the EU, as the COVID-19 situation is escalating, have focused on and prioritised, by all means, the prospect: COVID-19 treatments and vaccines.

EMA, on response to the urgent need for treatments and vaccines, has published initiatives encouraging developers of potential COVID-19 treatments and vaccines to make use of useful accelerating approaches. The initiatives summarise all regulatory flexibilities and possible MA pathways applicable during the pandemic. Beside the CMA, EMA has suggested other regulatory pathways including accelerated procedures, extension of MA or extension of indication, compassionate use programs and PRIME scheme (EMA, 2020c).

A review of the applications for marketing authorisation of COVID-19 treatments and vaccines submitted to EMA in the last few months, has shown that conditional marketing authorisation, combined with other unique strategies such as rolling review, rapid scientific advice was the main route to grant approval in the EU.

By the end of February 2021, three vaccines and one antiviral were successfully introduced into EU market via CMA.

Lately, a number of publications have discussed the critical role of the flexible regulatory procedures in facilitating the early access of patients to effective and safe medicines in times of pandemics (Boon *et al.*, 2010; Lumpkin and Lim, 2020; O'Brien *et al.*, 2020; Simpson *et al.*, 2020).

Moreover, a growing body of literature has underlined the great responsibility of the regulatory systems and has addressed the urgent need to strengthen and improve those systems (Stewart *et al.*, 2020; O'Brien, Lumsden and Macdonald, 2021). In an article (Soumyanarayanan *et al.*, 2020), the authors have analysed the role of Covid19 in revealing the weakness and testing the robustness of such regulatory systems.

A review has pictured EMA and FDA as role models of successful regulatory systems (O'Brien *et al.*, 2020). Not to mention the fact that millions of lives indeed rely on the decisions and the compromises made by the medicine regulators in this critical unprecedented situation.

With this in mind, an overview of the regulation and authorisation of medicinal products in the EU during the COVID-19 pandemic seemed to be rational. As it resembles a real time follow up of the responses, guidelines, recommendations and guidance which are based on an ongoing experience of the regulatory authorities in tackling a public health emergency.

As can be seen, the COVID-19 pandemic has painfully proved that the world was obviously underprepared for health threats in such large extent and that the risk of the emerging infectious diseases was underestimated. The public health institutions and organisations from all over the globe including EU are drawing lessons and insights from this crisis.

In August 2020, the WHO has published a working document for the good regulatory practices. The guideline addresses the principles which are relevant to the regulatory oversight of medicinal products. The nine principles are: legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency. In the context of public health emergencies, the flexibility is keen to be a key principle. According to WHO´s experts, regulatory activities should be rather flexible in order to contain the continuously changing or unforeseen situations and to support the innovation in development in pharma field. Fixable procedures also allow the timely response in case of public health emergencies (2022).

In an expert report, assembled by the European Commission´s Group of Chief Scientific Advisors (GCSA) and other joint advisors and published in November 2020, a set of recommendations to improve preparedness and management of pandemics are summarised.
The joint advisors suggest several strategies to strengthen regulatory systems.
According to the experts, this could be achieved by ensuring robust and equitable access of patients to critical medicinal products. The report also addresses the need of the EU to enhance the capacities and accelerate the different phases of clinical and pre-clinical studies, research and development, marketing authorisation and manufacturing of medicinal products in order to ensure the availability of crucial treatments and vaccines (2020e).

Another practical example is the European medicines agencies network strategy to 2025, where the lessons learned from the COVID-19 pandemic were taken into consideration aiming to enhance the regulation of medicines both nationally and at EU level in the future by dealing proactively with health emergencies. The pandemic experience has significantly influenced the strategy and the adopted policies within which it relies. Among the high-level goals and recommendations intended for the next 5 years and mended by the **COVID-19 learned lessons** are first, the need for more EU coordination and harmonisation of regulatory approaches during public health emergencies. Second, the importance of contentious periodic refinements of the regulatory tools and procedures to ensure the timely approval and the early access of patients to crucial medicines. Third, the importance of applying the regulatory flexibilities such as rolling review and rapid scientific advice not only in case of public health emergencies but also beyond that. Fourth, the incorporation of more digital tools, the diminution of regulatory burden as well as supporting of innovative approaches in development of medicinal products.
The strategy also underlines the power of the international alliances with relevant regulatory authorities and early collaboration between them. Such collaborations have proven to be of great value in generating robust and accurate data over a short period of time (HMA & EMA, 2020).

Pandemics and their burdens are known through human history. However, the advanced technologies and the innovative science available nowadays could be devoted to the expansion of research on the emerging infectious diseases, development of universal vaccines and upgrading the level of preparedness and awareness to major health threats.

COVID-19 situation has demonstrated the importance of international collaboration among the regulatory authorities as a key for regulatory harmonisation and pooling of scientific information. It has also proven the potency of digital tools to replace physical presence routines and meetings. Expectantly, COVID-19 experience will smooth the way for the future support of the innovative techniques in medicines and for understanding the sense of urgency to early access of patients suffering from serious or debilitating diseases to medicines (Stewart *et al.*, 2020; O'Brien, Lumsden and Macdonald, 2021).

Overall, the public health regulators should consider the COVID-19 crisis as a golden opportunity to improve and strengthen their regulatory systems and pay more attention to the innovative medicines. More innovative approaches and strategies which facilitate the early access of patients with urgent unmet medical needs to medicines should be taken into consideration.

An objective analysis of the regulatory activities implemented by public health authorities in the EU in order to evaluate the effectivity and productivity of these activities would be complementary to this work.

Limitations: Given the recent evolving situation, the data and information related to Covid-19 and the response of the regulatory authorities is continuously changing. Therefore the level of uncertainty, reliability and comprehensiveness of information is fluctuating and has occasionally affected the content of this work.

This work specifies the COVID-19 treatments and vaccines authorised in the EU or reviewed under Article 5(3) by EMA in the period between December 2020 and February 2021. In the first place, the main object of this work is reviewing the regulatory pathways for marketing authorisation during the pandemic and in the second place, the inclusion of all approved COVID-19 treatments and vaccines in the EU while the pandemic is not yet contained is not possible.

8 Bibliography

Adhikari, S. P. *et al.* (2020) 'Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review', *Infectious Diseases of Poverty*, 9, pp. 1–12. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1186/s40249-020-00646-x.

Agarwal, A. *et al.* (2020) 'Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)', *BMJ*, 371, p. m3939. doi: 10.1136/bmj.m3939.

AGES (2021) *AGES Dashboard COVID19*. Available at: https://covid19-dashboard.ages.at/?l=en (Accessed: 21 April 2021).

Ahmed, M. H. and Hassan, A. (2020) 'Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review', *Sn Comprehensive Clinical Medicine*, pp. 1–10. doi: 10.1007/s42399-020-00610-8.

Ahmed, S. F., Quadeer, A. A. and McKay, M. R. (2020) 'Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies', *Viruses*, 12(3), p. 254. doi: 10.3390/v12030254.

Arabi, Y. M. *et al.* (2017) 'Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome', *American Journal of Respiratory and Critical Care Medicine*, 197(6), pp. 757–767. doi: 10.1164/rccm.201706-1172OC.

Arnardottir, A. H. *et al.* (2011) 'Additional safety risk to exceptionally approved drugs in Europe?', *British Journal of Clinical Pharmacology*, 72(3), pp. 490–499. doi: https://doi.org/10.1111/j.1365-2125.2011.03995.x.

Avendaño-Solà, C. *et al.* (2020) 'Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial', *medRxiv*, p. 2020.08.26.20182444. doi: 10.1101/2020.08.26.20182444.

Awadasseid, A. *et al.* (2021) 'Effective drugs used to combat SARS-CoV-2 infection and the current status of vaccines, figure.', *Biomedicine & Pharmacotherapy*, 137, p. 111330. doi: 10.1016/j.biopha.2021.111330.

awan, M. (2020) *EMA activates health threat plan to support development of coronavirus therapies*. Available at: https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/ema-activates-health-threat-plan-to-support-development-of-coronavirus-therapies-56939836 (Accessed: 19 January 2021).

Baden, L. R. *et al.* (2020) 'Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine', *New England Journal of Medicine*. doi: 10.1056/NEJMoa2035389.

Baric, R. S. (2008) 'SARS-CoV: Lessons for global health', *Virus Research*, 133(1), pp. 1–3. doi: 10.1016/j.virusres.2007.03.024.

BASG (2015) *Compassionate use/Named Patient Use*, *BASG*. Available at: https://www.basg.gv.at/en/companies/medicinal-products/compassionate-use-1 (Accessed: 12 February 2021).

BASG (2017) 'Compassionate use programs in Austria'. Available at: https://www.basg.gv.at/fileadmin/redakteure/dateien/L_I216_Compassionate_use_AT_de.pdf (Accessed: 12 February 2021).

BASG (2020) *Medicine shortages*, *BASG*. Available at: https://www.basg.gv.at/en/market-surveillance/reporting/medicine-shortages (Accessed: 17 December 2020).

Bassareo, P. P. *et al.* (2020) 'Learning from the past in the COVID-19 era: rediscovery of quarantine, previous pandemics, origin of hospitals and national healthcare systems, and ethics in medicine', *Postgraduate Medical Journal*, 96(1140), pp. 633–638. doi: 10.1136/postgradmedj-2020-138370.

Baum, A. *et al.* (2020) 'Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies', *Science*, 369(6506), pp. 1014–1018. doi: 10.1126/science.abd0831.

Beigel, J. H. *et al.* (2020) 'Remdesivir for the Treatment of Covid-19 — Final Report', *New England Journal of Medicine*, 383(19), pp. 1813–1826. doi: 10.1056/NEJMoa2007764.

BIONTECH (2020) *BioNTech: mRNA technology: Mode of action of mRNA vaccines, Figure.*, *BioNTech*. Available at: https://www.biontech.de (Accessed: 19 April 2021).

Blake, K. V. *et al.* (2011) 'European Medicines Agency review of post-authorisation studies with implications for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance: Q 3.22,3.23 and 4.12', *Pharmacoepidemiology and Drug Safety*, 20(10), pp. 1021–1029. doi: https://doi.org/10.1002/pds.2209.

BMASGK (2020) *Sonderregelungen für Arzneimittel für die dauer der Pandemie mit COVID-19 RIS Dokument*. Available at: https://www.ris.bka.gv.at/Dokumente/BgblAuth/BGBLA_2020_II_377/BGBLA_2020_II_377.html (Accessed: 22 January 2021).

Bohk-Ewald, C., Dudel, C. and Myrskylä, M. (2020) 'A demographic scaling model for estimating the total number of COVID-19 infections', *International Journal of Epidemiology*, (dyaa198). doi: 10.1093/ije/dyaa198.

Böhning, D. *et al.* (2020) 'Estimating the undetected infections in the Covid-19 outbreak by harnessing capture–recapture methods', *International Journal of Infectious Diseases*, 97, pp. 197–201. doi: 10.1016/j.ijid.2020.06.009.

Boon, W. P. C. *et al.* (2010) 'Conditional Approval and Approval Under Exceptional Circumstances as Regulatory Instruments for Stimulating Responsible Drug Innovation in Europe', *Clinical Pharmacology & Therapeutics*, 88(6), pp. 848–853. doi: https://doi.org/10.1038/clpt.2010.207.

Boucaud-Maitre, D. and Altman, J.-J. (2016) 'Do the EMA accelerated assessment procedure and the FDA priority review ensure a therapeutic added value? 2006–2015: a cohort study', *European Journal of Clinical Pharmacology*, 72(10), pp. 1275–1281. doi: 10.1007/s00228-016-2104-3.

Bundes Amt für Sicherheit im Gesundheitswesen (2020) *Marketing authorisation & lifecycle*, *BASG*. Available at: https://www.basg.gv.at/en/companies/marketing-authorisation-life-cycle (Accessed: 17 December 2020).

Burwick, R. M. *et al.* (2020) 'Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019', *Clinical Infectious Diseases*, (ciaa1466). doi: 10.1093/cid/ciaa1466.

Cain, D. W. and Cidlowski, J. A. (2020) 'After 62 years of regulating immunity, dexamethasone meets COVID-19', *Nature Reviews. Immunology*, pp. 1–2. doi: 10.1038/s41577-020-00421-x.

Casadevall, A. and Pirofski, L. (2020) 'The convalescent sera option for containing COVID-19', *The Journal of Clinical Investigation*, 130(4), pp. 1545–1548. doi: 10.1172/JCI138003.

Cascio, A. *et al.* (2011) 'The socio-ecology of zoonotic infections', *Clinical Microbiology and Infection*, 17(3), pp. 336–342. doi: 10.1111/j.1469-0691.2010.03451.x.

CDC (2020) *Cases, Data, and Surveillance*, *Centers for Disease Control and Prevention*. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html (Accessed: 14 January 2021).

Chaikhouni, A. (2020) 'The new COVID-19 in context of historical pandemics.', *Heart Views*, 21(3), pp. 235–235.

Channappanavar, R. and Perlman, S. (2017) 'Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology', *Seminars in Immunopathology*, 39(5), pp. 529–539. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1007/s00281-017-0629-x.

Chaplin, S. (2020) 'Remdesivir: an antiviral for the treatment of COVID-19', *Prescriber (London, England)*, 31(7–8), pp. 31–33. doi: 10.1002/psb.1859.

Chitalia, V. C. and Munawar, A. H. (2020) 'A painful lesson from the COVID-19 pandemic: the need for broad-spectrum, host-directed antivirals', *Journal of Translational Medicine*, 18(1), p. 390. doi: 10.1186/s12967-020-02476-9.

CHMP (2018) 'EMA/CHMP/57760/2015, Rev.1: Enhanced early dialogue facilitate accelerated assessment priority medicines (PRIME)'. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf (Accessed: 20 February 2021).

Cho, A. *et al.* (2012) 'Synthesis and antiviral activity of a series of 1'-substituted 4-aza-7,9-dideazaadenosine C-nucleosides', *Bioorganic & Medicinal Chemistry Letters*, 22(8), pp. 2705–2707. doi: 10.1016/j.bmcl.2012.02.105.

CMDh (2020) 'Practical guidance of the CMDh for facilitating the handling of processes during the COVID-19 crisis'. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/COVID-19/CMDh_418_220_Rev1_05_2020_clean_-_PG_on_COVID-19_crisis.pdf (Accessed: 21 January 2021).

Consortium, W. S. trial *et al.* (2020) 'Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results', *medRxiv*, p. 2020.10.15.20209817. doi: 10.1101/2020.10.15.20209817.

CZARSKA-THORLEY, D. (2020a) *EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation (Accessed: 27 February 2021).

CZARSKA-THORLEY, D. (2020b) *EMA establishes task force to take quick and coordinated regulatory action related COVID-19 medicines*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-establishes-task-force-take-quick-coordinated-regulatory-action-related-covid-19-medicines (Accessed: 19 January 2021).

CZARSKA-THORLEY, D. (2020c) *EMA receives application for conditional authorisation of first COVID-19 treatment in the EU*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-receives-application-conditional-authorisation-first-covid-19-treatment-eu (Accessed: 26 February 2021).

CZARSKA-THORLEY, D. (2020d) *EMA receives application for marketing authorisation of Dexamethasone Taw COVID-19*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-receives-application-marketing-authorisation-dexamethasone-taw-covid-19 (Accessed: 24 January 2021).

CZARSKA-THORLEY, D. (2020e) *EMA starts rolling review of remdesivir for COVID-19*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-starts-rolling-review-remdesivir-covid-19 (Accessed: 26 February 2021).

CZARSKA-THORLEY, D. (2021a) *COVID-19 Vaccine Moderna*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-moderna (Accessed: 24 January 2021).

CZARSKA-THORLEY, D. (2021b) *EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab)*, *European Medicines Agency*. Available at:

https://www.ema.europa.eu/en/news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimab-imdevimab (Accessed: 3 March 2021).

CZARSKA-THORLEY, D. (2021c) *Extra dose from vials of Comirnaty COVID-19 vaccine*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/extra-dose-vials-comirnaty-covid-19-vaccine (Accessed: 24 January 2021).

Davies, N. G. *et al.* (2020) 'Age-dependent effects in the transmission and control of COVID-19 epidemics', *Nature Medicine*, 26(8), pp. 1205–1211. doi: 10.1038/s41591-020-0962-9.

De Keersmaecker, S. and Cassidy, D. (2020) *Coronavirus: Commission unveils EU vaccines strategy*, *European Commission - European Commission*. Available at: https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1103 (Accessed: 21 January 2021).

De Wit, E. *et al.* (2016) 'SARS and MERS: recent insights into emerging coronaviruses', *Nature Reviews. Microbiology*, 14(8), pp. 523–534. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1038/nrmicro.2016.81.

Deb, P., Molla, Md. M. A. and Saif-Ur-Rahman, K. M. (2021) 'An update to monoclonal antibody as therapeutic option against COVID-19', *Biosafety and Health*. doi: 10.1016/j.bsheal.2021.02.001.

Deen, J., Mengel, M. A. and Clemens, J. D. (2020) 'Epidemiology of cholera', *Vaccine*, 38, pp. A31–A40. doi: 10.1016/j.vaccine.2019.07.078.

Definition of PANDEMIC (2020). Available at: https://www.merriam-webster.com/dictionary/pandemic (Accessed: 12 January 2021).

EC (2006) *Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the council*. Available at: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf (Accessed: 27 January 2021).

EC (2007) 'Giudance on a new therapeutic indication for a well-established substance'. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/10%2520_5_%2520guideline_11-2007_en.pdf (Accessed: 18 February 2021).

EC (2019) 'Guidance on the categorisation of Extension Applications (EA) versus Variations Applications (V)'. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/v2c_ea_v__10_2003_en.pdf (Accessed: 19 February 2021).

EC (2020a) *Daily News 03 / 07 / 2020*, *European Commission - European Commission*. Available at: https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266 (Accessed: 14 January 2021).

EC (2020b) *First safe and effective vaccine against COVID-19*, *European Commission - European Commission*. Available at: https://ec.europa.eu/commission/presscorner/detail/en/IP_20_2466 (Accessed: 14 January 2021).

EC (2020c) 'guidance on the collection and transfusion of convalescent covid19 plasma'. Available at: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/guidance_plasma_covid19_en.pdf (Accessed: 25 February 2021).

EC (2020d) *How are vaccines developed, authorised and put on the market?*, *European Commission - European Commission*. Available at: https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans/how-are-vaccines-developed-authorised-and-put-market_en (Accessed: 4 March 2021).

EC (2020e) 'Improving pandemic preparefdness and management'. Available at: https://ec.europa.eu/info/sites/info/files/research_and_innovation/groups/sam/jointopinion_improvingpandemicpreparednessandmanagement_november-2020.pdf (Accessed: 12 April 2021).

EC (2021) *Second safe and effective vaccine against COVID-19*, *European Commission - European Commission*. Available at: https://ec.europa.eu/commission/presscorner/detail/en/IP_21_3 (Accessed: 14 January 2021).

ECDC (2020) *Risk factors and risk groups*, *European Centre for Disease Prevention and Control*. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/epidemiology (Accessed: 30 December 2020).

ECDC (2021) *COVID-19 situation update for the EU/EEA, as of 21 April 2021*, *European Centre for Disease Prevention and Control*. Available at: https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea (Accessed: 21 April 2021).

EDQM (2020a) *COVID-19 update: Ph. Eur. and British Pharmacopoeia working together to offer free access to supportive pharmacopoeial texts | EDQM - European Directorate for the Quality of Medicines*. Available at: https://www.edqm.eu/en/news/covid-19-update-ph-eur-and-british-pharmacopoeia-working-together-offer-free-access-supportive (Accessed: 22 January 2021).

EDQM (2020b) *EDQM initiatives in the context of COVID-19 vaccines and therapies | EDQM - European Directorate for the Quality of Medicines*. Available at: https://www.edqm.eu/en/edqm-initiatives-context-covid-19-vaccines-and-therapies (Accessed: 17 December 2020).

EDQM (2020c) *EDQM provides COVID-19 vaccine developers with free access to quality standards applicable in Europe | EDQM - European Directorate for the Quality of Medicines*. Available at: https://www.edqm.eu/en/news/edqm-provides-covid-19-vaccine-developers-free-access-quality-standards-applicable-europe (Accessed: 22 January 2021).

EDQM (2020d) *EDQM releases updated European Pharmacopoeia vaccines package for COVID-19 vaccine developers | EDQM - European Directorate for the Quality of Medicines*.

Available at: https://www.edqm.eu/en/news/edqm-releases-updated-european-pharmacopoeia-vaccines-package-covid-19-vaccine-developers (Accessed: 22 January 2021).

EDQM (2020e) *Prioritisation of activities related to CEPs during COVID-19 contingency measures period | EDQM - European Directorate for the Quality of Medicines*. Available at: https://www.edqm.eu/en/news/prioritisation-activities-related-ceps-during-covid-19-contingency-measures-period (Accessed: 22 January 2021).

EMA (2007) 'EMEA/27170/2006: Guideline on Compassionate use of Medicinal Products'.

EMA (2010) 'EMEA/72144/2006: Questions and answers on the compassionate use of medicines in the european union'. Available at: https://www.ema.europa.eu/en/documents/other/questions-answers-compassionate-use-medicines-european-union_en-0.pdf (Accessed: 8 February 2021).

EMA (2014) 'EMA/PDCO/179892/2011 Rev. 2: Questions and answers on the procedure of PIP compliance verification at EMA, and on paediatric rewards'. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-procedure-paediatric-investigation-plan-compliance-verification-european-medicines_en.pdf (Accessed: 20 February 2021).

EMA (2016a) *EMA/471951/2016: conditional marketing authorisation report ten years experience european medicines agency*. London: European Medicine Agency. Available at: https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf (Accessed: 3 February 2021).

EMA (2016b) 'EMA/716925/2016 The European regulatory system for medicines'. Available at: https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf.

EMA (2016c) 'EMA/CHMP/671361/2015 Rev. 1: Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004'.

EMA (2018a) *Accelerated assessment*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment (Accessed: 6 February 2021).

EMA (2018b) *Compassionate use*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use (Accessed: 8 February 2021).

EMA (2018c) *Conditional marketing authorisation*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (Accessed: 27 January 2021).

EMA (2018d) 'EMA/191104/2015: European medicines Agency Guidance applicants seeking access prime scheme'. Available at: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf (Accessed: 20 February 2021).

EMA (2018e) *Marketing authorisation*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation (Accessed: 26 January 2021).

EMA (2018f) *PRIME: priority medicines*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines (Accessed: 20 February 2021).

EMA (2018g) *Q&A: Type II variations vs Extension applications*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/variations/type-ii-variations/qa-type-ii-variations-vs-extension-applications (Accessed: 19 February 2021).

EMA (2018h) *Referral procedures*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures (Accessed: 2 March 2021).

EMA (2020a) 'EMA/4260/2001 Rev.10: European Medicines Agency Guidance applicants seeking scientific advice protocol assistance'. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf (Accessed: 19 February 2021).

EMA (2020b) 'EMA/134143/2020: Decision of the Executive Director on fee reductions for scientific advice requests on products for the prevention and/or treatment of COVID-19', p. 2.

EMA (2020c) 'EMA/213341/2020: ema initiatives for acceleration of development support and evaluation procedures for covid-19 treatments vaccines'. Available at: https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf (Accessed: 27 January 2021).

EMA (2020d) *infographic-fast-track-procedures-treatments-vaccines-covid-19_en.pdf*. Available at: https://www.ema.europa.eu/en/documents/leaflet/infographic-fast-track-procedures-treatments-vaccines-covid-19_en.pdf (Accessed: 14 February 2021).

EMA (2020e) *Pre-authorisation guidance: 2.8 Is my product eligible for an accelerated assessment?*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance (Accessed: 8 February 2021).

EMA (2021a) ‘comirnaty EPAR product information’. Available at: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf (Accessed: 8 March 2021).

EMA (2021b) ‘covid-19 vaccine AstraZeneca: EPAR product information’. Available at: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-astrazeneca-epar-product-information_en.pdf (Accessed: 14 March 2021).

EMA (2021c) ‘covid-19 vaccine moderna EPAR product information’. Available at: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf (Accessed: 12 March 2021).

EMA (2021d) ‘EMEA-H-19984/03 Rev.89: European Medicines Agency post authorisation procedural advice users centralised procedure’. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf (Accessed: 18 February 2021).

EMA (2021e) ‘REGN-COV2 conditions of use conditions of distribution and patients targeted and conditions for safety’. Available at: https://www.ema.europa.eu/en/documents/referral/regn-cov2-antibody-combination-casirivimab/imdevimab-covid-19-conditions-use-conditions-distribution-patients-targeted-conditions-safety_en.pdf (Accessed: 3 March 2021).

EMA/CHMP (2016) *EMA/CHMP/509951/2006, Rev.1: Guideline on the scientific application and practical arrangements necessary to implement Regulation (EC) No 507/2006 conditional marketing authorisation for medicinal products human use falling within scope of ...*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/guideline-scientific-application-practical-arrangements-necessary-implement-regulation-ec-no-5072006 (Accessed: 30 January 2021).

Emary, K. R. W. *et al.* (2021) *Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 VOC 202012/01 (B.1.1.7)*. SSRN Scholarly Paper ID 3779160. Rochester, NY: Social Science Research Network. doi: 10.2139/ssrn.3779160.

European Commission (2020) ‘communication from the Commission EU Strategy for COVID-19 vaccines’. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0245&from=EN (Accessed: 21 January 2021).

European Medicines Agency (2018a) *EMA/863454/2018: EMA plan for emerging health threats*. Available at: https://www.ema.europa.eu/en/documents/other/ema-plan-emerging-health-threats_en.pdf (Accessed: 19 January 2021).

European Medicines Agency (2018b) *History of EMA*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/about-us/history-ema (Accessed: 26 January 2021).

European Medicines Agency (2020a) ‘EMA/166423/2020 Mandate, objectives and rules of procedure of the COVID-19 EMA pandemic Task Force (COVID-ETF)’. Available at:

https://www.ema.europa.eu/en/documents/other/mandate-objectives-rules-procedure-covid-19-ema-pandemic-task-force-covid-etf_en.pdf (Accessed: 19 January 2021).

European Medicines Agency (2020b) 'EMA/199630/2020: european medicines regulatory network covid-19 business continuity plan'. Available at: https://www.ema.europa.eu/en/documents/other/european-medicines-regulatory-network-covid-19-business-continuity-plan_en.pdf (Accessed: 19 January 2021).

European Medicines Agency (2020c) *EMA/336621/2020 eSubmissions Web UI- Release-Notes*. Available at: http://esubmission.ema.europa.eu/gateway/eSubmissions%20Web%20UI-%20ReleaseNotes.pdf (Accessed: 24 January 2021).

European Medicines Agency, European Commission, and Head of Medicine Agencies (2020a) 'Guidance on the management of clinical trials during the COVID-19 (Corona Virus) pandemic'. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (Accessed: 16 December 2020).

European Medicines Agency, European Commission, and Head of Medicine Agencies (2020b) 'Notice to stakeholders: Q & A on regulatory Expectations for medicinal products for human use during the COVID-19 pandemic.' Available at: https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf (Accessed: 14 December 2020).

European Parliment (2006) *Regulation (EC) No 1901/2006 on medcicinal products for paediatric use*. Available at: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (Accessed: 20 February 2021).

European Parliment and Council of European Union (2004) *B Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*. Available at: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (Accessed: 8 February 2021).

European Parliment and The Conuncil (2004) *Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF (Accessed: 6 February 2021).

FDA (2021) 'Convalescent Plasma EUA letter of authorization'. Available at: https://www.fda.gov/media/141477/download (Accessed: 15 March 2021).

FITT, H. (2020) *HMA/EMA statement on approval of vaccines*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/hmaema-statement-approval-vaccines (Accessed: 12 April 2021).

Florindo, H. F. *et al.* (2020) 'Immune-mediated approaches against COVID-19', *Nature Nanotechnology*, 15(8), pp. 630–645. doi: 10.1038/s41565-020-0732-3.

FRANCISCO, E. M. (2020) *EMA provides recommendations on compassionate use of remdesivir for COVID-19*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19 (Accessed: 24 January 2021).

GLANVILLE, D. (2020a) *COVID-19 vaccines: development, evaluation, approval and monitoring*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring (Accessed: 4 March 2021).

GLANVILLE, D. (2020b) *COVID-19 vaccines: development, evaluation, approval and monitoring, figure*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (Accessed: 22 April 2021).

GLANVILLE, D. (2021a) *EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu (Accessed: 12 March 2021).

GLANVILLE, D. (2021b) *Treatments and vaccines for COVID-19: authorised medicines*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-authorised-medicines (Accessed: 5 February 2021).

GLANVILLE, D. (2021c) *Treatments and vaccines for COVID-19: medicines under evaluation*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-medicines-under-evaluation (Accessed: 14 February 2021).

Grasselli, G. *et al.* (2020) 'Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy', *JAMA*, 323(16), p. 1574. doi: 10.1001/jama.2020.5394.

Grein, J. *et al.* (2020) 'Compassionate Use of Remdesivir for Patients with Severe Covid-19', *New England Journal of Medicine*. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1056/NEJMoa2007016.

Guarner, J. (2020) 'Three Emerging Coronaviruses in Two Decades: The Story of SARS, MERS, and Now COVID-19', *American Journal of Clinical Pathology*, 153(4), pp. 420–421. doi: 10.1093/ajcp/aqaa029.

Hansen, J. *et al.* (2020) 'Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail, Figure.', *Science*, 369(6506), pp. 1010–1014. doi: 10.1126/science.abd0827.

Head of Medicine Agencies (no date) *Heads of Medicines Agencies: About HMA*. Available at: https://www.hma.eu/ (Accessed: 17 January 2021).

Heemstra, H. E. *et al.* (2010) 'Safety-Related Regulatory Actions for Orphan Drugs in the US and EU', *Drug Safety*, 33(2), pp. 127–137. doi: 10.2165/11319870-000000000-00000.

HMA & EMA (2020) 'european medicines agencies network strategy to 2025 protecting public health at a time of rapid change'. Available at: https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf (Accessed: 12 April 2021).

Hoekman, J. *et al.* (2015) 'Use of the conditional marketing authorization pathway for oncology medicines in Europe', *Clinical Pharmacology & Therapeutics*, 98(5), pp. 534–541. doi: 10.1002/cpt.174.

Horby, P. *et al.* (2020) 'Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report', *The New England Journal of Medicine*. doi: 10.1056/NEJMoa2021436.

HRABOVSZKI, G. (2020a) *Call to pool research resources into large multi-centre, multi-arm clinical trials generate sound evidence on COVID-19 treatments*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/call-pool-research-resources-large-multi-centre-multi-arm-clinical-trials-generate-sound-evidence (Accessed: 24 January 2021).

HRABOVSZKI, G. (2020b) *COVID-19: latest updates*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-latest-updates (Accessed: 27 January 2021).

HRABOVSZKI, G. (2020c) *EMA to support development of vaccines and treatments for novel coronavirus disease (COVID-19)*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-support-development-vaccines-treatments-novel-coronavirus-disease-covid-19 (Accessed: 26 January 2021).

HRABOVSZKI, G. (2020d) *EMA's governance during COVID-19 pandemic*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic (Accessed: 15 December 2020).

Huang, C. *et al.* (2020) 'Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China', *The Lancet*, 395(10223), pp. 497–506. doi: 10.1016/S0140-6736(20)30183-5.

Jones, K. E. *et al.* (2008) 'Global trends in emerging infectious diseases', *Nature*, 451(7181), pp. 990–993. doi: 10.1038/nature06536.

Karesh, W. B. *et al.* (2012) 'Ecology of zoonoses: natural and unnatural histories', *The Lancet*, 380(9857), pp. 1936–45. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1016/S0140-6736(12)61678-X.

Kliger, Y. and Levanon, E. Y. (2003) 'Cloaked similarity between HIV-1 and SARS-CoV suggests an anti-SARS strategy', *BMC Microbiology*, 3(1), p. 20. doi: 10.1186/1471-2180-3-20.

La Rosa, G. *et al.* (2020) 'Coronavirus in water environments: Occurrence, persistence and concentration methods - A scoping review', *Water Research*, 179, p. 115899. doi: 10.1016/j.watres.2020.115899.

Lee, N. *et al.* (2004) 'Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients', *Journal of Clinical Virology*, 31(4), pp. 304–309. doi: 10.1016/j.jcv.2004.07.006.

Li, R. *et al.* (2020) 'Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2)', *Science (New York, N.Y.)*, 368(6490), pp. 489–493. doi: 10.1126/science.abb3221.

Libster, R. *et al.* (2021) 'Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults', *New England Journal of Medicine*, 384(7), pp. 610–618. doi: 10.1056/NEJMoa2033700.

Lippi, D., Gotuzzo, E. and Caini, S. (2016) 'Cholera', *Microbiology Spectrum*, 4(4). doi: 10.1128/microbiolspec.PoH-0012-2015.

Liu, Y.-C., Kuo, R.-L. and Shih, S.-R. (2020) 'COVID-19: The first documented coronavirus pandemic in history.', *Biomedical journal*, 43(4), pp. 328–333. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1016/j.bj.2020.04.007.

Lu, R. *et al.* (2020) 'Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding', *The Lancet*, 395(10224), pp. 565–574. doi: 10.1016/S0140-6736(20)30251-8.

Lumpkin, M. M. and Lim, J. C. W. (2020) 'Pandemic Best Regulatory Practices: An Urgent Need in the COVID-19 Pandemic', *Clinical Pharmacology & Therapeutics*, 108(4), pp. 703–705. doi: https://doi.org/10.1002/cpt.1932.

Magro, G. (2020) 'COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking', *Virus Research*, 286, p. 198070. doi: 10.1016/j.virusres.2020.198070.

Manski, C. F. and Molinari, F. (2021) 'Estimating the COVID-19 infection rate: Anatomy of an inference problem', *Journal of Econometrics*, 220(1), pp. 181–192. doi: 10.1016/j.jeconom.2020.04.041.

Mitre-Aguilar, I. B., Cabrera-Quintero, A. J. and Zentella-Dehesa, A. (2015) 'Genomic and non-genomic effects of glucocorticoids: implications for breast cancer', *International Journal of Clinical and Experimental Pathology*, 8(1), pp. 1–10.

Mulangu, S. *et al.* (2019) 'A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics', *New England Journal of Medicine*, 381(24), pp. 2293–2303. doi: 10.1056/NEJMoa1910993.

National Academies of Sciences, E. *et al.* (2019) *Exploring Lessons Learned from a Century of Outbreaks: Readiness for 2030: Proceedings of a Workshop*. Washington, D.C: National Academies Press. doi: 10.17226/25391.

National Center for Biotechnology Information (2021) *Dexamethasone*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/5743 (Accessed: 28 February 2021).

NewsRX LLC (ed.) (2020) 'Pharming announces the publication of data from a compassionate use programme of RUCONEST® in COVID-19 patients in a peer-reviewed journal.', *Medical Letter on the CDC & FDA*, pp. 1237–1237.

NIH (2020) *NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19 | NIH: National Institute of Allergy and Infectious Diseases*. Available at: https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19 (Accessed: 26 February 2021).

O'Brien, J. *et al.* (2020) 'Building a Better Approach for the Benefit of Patients: 10 Pillars to Strengthen Regulatory Review Systems Globally', *Therapeutic Innovation & Regulatory Science*, 54(2), pp. 283–292. doi: 10.1007/s43441-019-00055-9.

O'Brien, J., Lumsden, R. and Macdonald, J. (2021) 'Strengthening regulatory systems for medicines in a changed world: where do we go from here?', *BMJ Global Health*, 6(1), p. e004680. doi: 10.1136/bmjgh-2020-004680.

Office of Science and Innovation, London (2006) *Infectious diseases: preparing for the future. Executive Summary*, *GOV.UK*. Available at: https://www.gov.uk/government/publications/infectious-diseases-preparing-for-the-future (Accessed: 12 January 2021).

Ogris, G. and Oberhuber, F. (2020) 'Spread of SARS-CoV-2 in Austria', *SORA Institute for Social Reasearch and Consulting*, p. 41.

Ortolani, C. and Pastorello, E. A. (2020) 'Hydroxychloroquine and dexamethasone in COVID-19: who won and who lost?', *Clinical and Molecular Allergy*, 18(1), p. 17. doi: 10.1186/s12948-020-00132-7.

Padda, I. S. and Parmar, M. (2021) 'COVID (SARS-COV-2) Vaccine', in *StatPearls*. Treasure Island (FL): StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/books/NBK567793/ (Accessed: 7 March 2021).

Pardi, N. *et al.* (2018) 'Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses', *Journal of Experimental Medicine*, 215(6), pp. 1571–1588. doi: 10.1084/jem.20171450.

Park, M., Thwaites, R. S. and Openshaw, P. J. M. (2020) 'COVID-19: Lessons from SARS and MERS', *European Journal of Immunology*, 50(3), pp. 308–311. doi: https://doi.org/10.1002/eji.202070035.

Pathak, E. B. (2020) 'Convalescent plasma is ineffective for covid-19', *BMJ*, 371, p. m4072. doi: 10.1136/bmj.m4072.

Phipps, S. J., Grafton, R. Q. and Kompas, T. (2020) 'Robust estimates of the true (population) infection rate for COVID-19: a backcasting approach', *Royal Society Open Science*. doi: 10.1098/rsos.200909.

PINHO, A. C. (2020a) *EMA receives application for conditional marketing authorisation of COVID-19 mRNA vaccine BNT162b2*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-receives-application-conditional-marketing-authorisation-covid-19-mrna-vaccine-bnt162b2 (Accessed: 24 January 2021).

PINHO, A. C. (2020b) *EMA recommends first COVID-19 vaccine for authorisation in the EU*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu (Accessed: 11 January 2021).

PINHO, A. C. (2020c) *EMA starts rolling review of Janssen's COVID-19 vaccine Ad26.COV2.S*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-starts-rolling-review-janssens-covid-19-vaccine-ad26cov2s (Accessed: 24 January 2021).

PINHO, A. C. (2020d) *Transparency: exceptional measures for COVID-19 medicines*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines (Accessed: 15 March 2021).

PINHO, A. C. (2020e) *Update on remdesivir - EMA will evaluate new data from Solidarity trial*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/update-remdesivir-ema-will-evaluate-new-data-solidarity-trial (Accessed: 27 February 2021).

PINHO, A. C. (2021a) *AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low platelets*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood (Accessed: 23 April 2021).

PINHO, A. C. (2021b) *COVID-19 Vaccine Janssen: assessment of very rare cases unusual blood clots with low platelets continues*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-assessment-very-rare-cases-unusual-blood-clots-low-platelets-continues (Accessed: 24 April 2021).

PINHO, A. C. (2021c) *EMA preparing guidance to tackle COVID-19 variants*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-preparing-guidance-tackle-covid-19-variants (Accessed: 11 March 2021).

PINHO, A. C. (2021d) *EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu (Accessed: 14 March 2021).

PINHO, A. C. (2021e) *EMA recommends COVID-19 Vaccine Janssen for authorisation in the EU*, *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-janssen-authorisation-eu (Accessed: 24 April 2021).

Polack, F. P. *et al.* (2020) 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine', *New England Journal of Medicine*. doi: 10.1056/NEJMoa2034577.

Porta, M. (2014) *A Dictionary of Epidemiology*. Oxford: University Press, Incorporated, Oxford University Press.

Publications Office of the European Union (2008) *Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Text with EEA relevance), CELEX1*. Publications Office of the European Union. Available at: http://op.europa.eu/en/publication-detail/-/publication/6b6ad3b2-5608-499e-882d-0010dd1921e1/language-en (Accessed: 18 February 2021).

Publications Office of the European Union (2013) *Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures, CELEX1*. Publications Office of the European Union. Available at: http://op.europa.eu/en/publication-detail/-/publication/b196a096-0337-11e3-a352-01aa75ed71a1 (Accessed: 18 February 2021).

Puplications Office of the European Union (2012) 'Commission Regulation (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal productsText with EEA relevance', p. 11.

Rabaa, M. A. *et al.* (2015) 'The Vietnam Initiative on Zoonotic Infections (VIZIONS): A Strategic Approach to Studying Emerging Zoonotic Infectious Diseases', *EcoHealth*, 12(4), pp. 726–735. doi: 10.1007/s10393-015-1061-0.

RECOVERY (2021) *RECOVERY trial closes recruitment to convalescent plasma treatment for patients hospitalised with COVID-19 — RECOVERY Trial*. Available at: https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19 (Accessed: 15 March 2021).

Riccardo, F. *et al.* (2020) 'Epidemiological characteristics of COVID-19 cases in Italy and estimates of the reproductive numbers one month into the epidemic', *medRxiv*, p. 2020.04.08.20056861. doi: 10.1101/2020.04.08.20056861.

Richardson, C., Bhagani, S. and Pollara, G. (2020) 'Antiviral treatment for COVID-19: the evidence supporting remdesivir', *Clinical Medicine*, 20(6), pp. e215–e217. doi: 10.7861/clinmed.2020-0524.

Rothan, H. A. and Byrareddy, S. N. (2020) 'The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak', *Journal of Autoimmunity*, 109, p. 102433. doi: 10.1016/j.jaut.2020.102433.

RTDs Group (2021) *APEPTICO - Innovation in peptide drugs - Solnatide in Horizon 2020 - Vienna, Austria*. Available at: http://www.apeptico.com/index-solnatide_in_horizon_2020 (Accessed: 13 February 2021).

Russell, C. D., Millar, J. E. and Baillie, J. K. (2020) 'Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury', *The Lancet*, 395(10223), pp. 473–475. doi: 10.1016/S0140-6736(20)30317-2.

Sahin, U. *et al.* (2020) 'BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans', *medRxiv*, p. 2020.12.09.20245175. doi: 10.1101/2020.12.09.20245175.

Saint-Raymond, A. *et al.* (2020) 'Remdesivir emergency approvals: a comparison of the U.S., Japanese, and EU systems', *Expert Review of Clinical Pharmacology*, 13(10), pp. 1095–1101. doi: 10.1080/17512433.2020.1821650.

sciensano (2020) 'COVID-19 Fact Sheet, Version 7'. Sciensano. Available at: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_fact_sheet_ENG.pdf (Accessed: 15 January 2021).

Semenza, J. C. *et al.* (2013) 'Linking Environmental Drivers to Infectious Diseases: The European Environment and Epidemiology Network', *PLOS Neglected Tropical Diseases*, 7(7), p. e2323. doi: 10.1371/journal.pntd.0002323.

Semenza, J. C. (2015) 'Prototype Early Warning Systems for Vector-Borne Diseases in Europe', *International Journal of Environmental Research and Public Health*, 12(6), pp. 6333–6351. doi: 10.3390/ijerph120606333.

Semenza, J. C. *et al.* (2016) 'Determinants and Drivers of Infectious Disease Threat Events in Europe - Volume 22, Number 4—April 2016 - Emerging Infectious Diseases journal - CDC'. doi: 10.3201/eid2204.151073.

Seth Flaxman, Swapnil Mishra, Axel Gandy et a (2020) *Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries*, *Imperial College London*. doi: https://doi.org/10.25561/77731.

Shang, L. *et al.* (2020) 'On the use of corticosteroids for 2019-nCoV pneumonia', *The Lancet*, 395(10225), pp. 683–684. doi: 10.1016/S0140-6736(20)30361-5.

Sharma, O. *et al.* (2020) 'A Review of the Progress and Challenges of Developing a Vaccine for COVID-19', *Frontiers in Immunology*, 11. doi: 10.3389/fimmu.2020.585354.

Sheahan, T. P. *et al.* (2017) 'Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses', *Science Translational Medicine*, 9(396). doi: 10.1126/scitranslmed.aal3653.

Simonovich, V. A. *et al.* (2021) 'A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia', *New England Journal of Medicine*, 384(7), pp. 619–629. doi: 10.1056/NEJMoa2031304.

Simpson, S. *et al.* (2020) 'Navigating facilitated regulatory pathways during a disease X pandemic', *npj Vaccines*, 5(1), pp. 1–9. doi: 10.1038/s41541-020-00249-5.

Singh, S. *et al.* (2020) 'Allogeneic cardiosphere-derived cells (CAP-1002) in critically ill COVID-19 patients: compassionate-use case series', *Basic Research in Cardiology*, 115(4), p. 36. doi: 10.1007/s00395-020-0795-1.

Sou, H. (2010) 'EU compassionate use programmes (CUPs): regulatory framework and points to consider before CUP implementation', *Pharmaceutical Medicine*, 24(4), pp. 223–230.

Soumyanarayanan, U. *et al.* (2020) 'The COVID-19 crisis as an opportunity to strengthen global regulatory coordination for sustained enhanced access to diagnostics and therapeutics', *Clinical and Translational Science*, n/a(n/a). doi: https://doi.org/10.1111/cts.12954.

Stewart, J. *et al.* (2020) 'COVID-19: A Catalyst to Accelerate Global Regulatory Transformation', *Clinical Pharmacology & Therapeutics*. doi: 10.1002/cpt.2046.

Suk, J. E., Lyall, C. and Tait, J. (2008) 'Mapping the future dynamics of disease transmission: risk analysis in the United Kingdom Foresight Programme on the detection and identification of infectious diseases', *Eurosurveillance*, 13(44), p. 19021. doi: 10.2807/ese.13.44.19021-en.

Suk, J. E. and Semenza, J. C. (2011) 'Future Infectious Disease Threats to Europe', *American Journal of Public Health*, 101(11), pp. 2068–2079. doi: 10.2105/AJPH.2011.300181.

Sumanth Khadke *et al.* (2020) 'Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: a review of the phases of illness and therapeutic agents', *Virology journal*, 17(1), pp. 1–154. doi: 10.1186/s12985-020-01415-w.

Taylor, L. H., Latham, S. M. and Woolhouse, M. E. (2001) 'Risk factors for human disease emergence.', *Philosophical Transactions of the Royal Society B: Biological Sciences*, 356(1411), pp. 983–989. doi: 10.1098/rstb.2001.0888.

Tumban, E. (2020) 'Lead SARS-CoV-2 Candidate Vaccines: Expectations from Phase III Trials and Recommendations Post-Vaccine Approval', *Viruses*, 13(1). doi: 10.3390/v13010054.

University of OXFORD (2020) *About the Oxford COVID-19 vaccine, Figure.* Available at: https://www.research.ox.ac.uk/Article/2020-07-19-the-oxford-covid-19-vaccine (Accessed: 19 April 2021).

University of OXFORD (2021) *Tocilizumab reduces deaths in patients hospitalised with COVID-19 — RECOVERY Trial*. Available at: https://www.recoverytrial.net/news/tocilizumab-reduces-deaths-in-patients-hospitalised-with-covid-19 (Accessed: 25 February 2021).

Voysey, M. *et al.* (2021) 'Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK', *The Lancet*, 397(10269), pp. 99–111. doi: 10.1016/S0140-6736(20)32661-1.

Walsh, E. E. *et al.* (2020) 'Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates', *New England Journal of Medicine*, 383(25), pp. 2439–2450. doi: 10.1056/NEJMoa2027906.

Wang, Yeming *et al.* (2020) 'Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial', *The Lancet*, 395(10236), pp. 1569–1578. doi: 10.1016/S0140-6736(20)31022-9.

Weinreich, D. M. *et al.* (2020) 'REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19', *New England Journal of Medicine*. doi: 10.1056/NEJMoa2035002.

WHO (2003a) *WHO | Cumulative Number of Reported Probable Cases of SARS*, *WHO*. World Health Organization. Available at: https://www.who.int/csr/sars/country/2003_07_11/en/ (Accessed: 13 January 2021).

WHO (2003b) *WHO | Update 95 - SARS: Chronology of a serial killer*, *WHO*. World Health Organization. Available at: https://www.who.int/csr/don/2003_07_04/en/ (Accessed: 28 December 2020).

WHO (2010a) *WHO | Pandemic (H1N1) 2009 - update 112*, *WHO*. World Health Organization. Available at: https://www.who.int/csr/don/2010_08_06/en/ (Accessed: 12 January 2021).

WHO (2010b) *WHO | What is a pandemic?*, *WHO*. World Health Organization. Available at: http://www.who.int/csr/disease/swineflu/frequently_asked_questions/pandemic/en/ (Accessed: 22 December 2020).

WHO (2020a) 'Corticosteriods for COVID-19 guidance'. Available at: https://apps.who.int/iris/bitstream/handle/10665/334125/WHO-2019-nCoV-Corticosteroids-2020.1-eng.pdf (Accessed: 23 December 2020).

WHO (2020b) *Listings of WHO's response to COVID-19*. Available at: https://www.who.int/news/item/29-06-2020-covidtimeline (Accessed: 14 January 2021).

WHO (2020c) *Prioritizing diseases for research and development in emergency contexts*. Available at: https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts (Accessed: 12 April 2021).

WHO (2020d) *WHO | Middle East respiratory syndrome coronavirus (MERS-CoV) – The Kingdom of Saudi Arabia*, *WHO*. World Health Organization. Available at: http://www.who.int/csr/don/24-february-2020-mers-saudi-arabia/en/ (Accessed: 13 January 2021).

WHO (2020e) *WHO announces COVID-19 outbreak a pandemic*. Available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic (Accessed: 22 December 2020).

WHO (2021a) 'Background document on the AZD1222 vaccine against COVID-19'. Available at: https://apps.who.int/iris/bitstream/handle/10665/339882/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-background-2021.2-eng.pdf (Accessed: 14 March 2021).

WHO (2021b) *Maintaining a safe and adequate blood supply and collecting convalescent plasma in the context of the COVID-19 pandemic*. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-BloodSupply-2021-1 (Accessed: 15 March 2021).

WHO (2021c) *Virus origin / Origins of the SARS-CoV-2 virus*. Available at: https://www.who.int/health-topics/coronavirus/origins-of-the-virus (Accessed: 12 April 2021).

WHO (2021d) *WHO Coronavirus (COVID-19) Dashboard*. Available at: https://covid19.who.int (Accessed: 21 April 2021).

WHO (2022) 'Good regulatory practices for regulatory oversight of medical products-working document'. Available at: https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas16-686-rev-3-good-regulatory-practices-medical-products.pdf?sfvrsn=ccb041db_2 (Accessed: 12 April 2021).

WHO Zoonoses (2020) *WHO*. Available at: https://www.who.int/news-room/fact-sheets/detail/zoonoses (Accessed: 11 January 2021).

WHO/Europe (2020) *EUR/RC70/Inf.Doc./7 A timeline of WHO's response to COVID-19 in the WHO European Region*. Available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2020/eurrc70inf.doc.7-a-timeline-of-whos-response-to-covid-19-in-the-who-european-region (Accessed: 14 January 2021).

WHO/Europe (2021) 'Fact sheet for health workers: Comiranty pfizer/BioNTech BNT162b2 vaccine.' Available at: https://apps.who.int/iris/bitstream/handle/10665/339681/WHO-EURO-2021-1964-41715-57093-eng.pdf?sequence=1&isAllowed=y (Accessed: 11 March 2021).

Wilcox, B. A. and Gubler, D. J. (2005) 'Disease ecology and the global emergence of zoonotic pathogens', *Environmental Health and Preventive Medicine*, 10(5), p. 263. doi: 10.1007/BF02897701.

Woolhouse, M. E. J. and Gowtage-Sequeria, S. (2005) 'Host Range and Emerging and Reemerging Pathogens', *Emerging Infectious Diseases*, 11(12), pp. 1842–1847. doi: 10.3201/eid1112.050997.

World Health Organization (2020) 'mRNA vaccines against COVID-19: Pfizer-BioNTech COVID-19 vaccine BNT162b2: prepared by the Strategic Advisory Group of Experts (SAGE) on immunization working group on COVID-19 vaccines.' Available at: https://apps.who.int/iris/handle/10665/338096 (Accessed: 11 March 2021).

Wu, J. T. *et al.* (2020) 'Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China', *Nature Medicine*, 26(4), pp. 506–510. doi: 10.1038/s41591-020-0822-7.

Wu, J. T., Leung, K. and Leung, G. M. (2020) 'Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study', *The Lancet*, 395(10225), pp. 689–697. doi: 10.1016/S0140-6736(20)30260-9.

Wu, K., Werner, A. P., Moliva, J. I., *et al.* (2021) 'mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants', *bioRxiv*, p. 2021.01.25.427948. doi: 10.1101/2021.01.25.427948.

Wu, K., Werner, A. P., Koch, M., *et al.* (2021) 'Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine — Preliminary Report', *New England Journal of Medicine*, 0(0), p. null. doi: 10.1056/NEJMc2102179.

Xia, X. *et al.* (2020) 'Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion', *Blood*, 136(6), pp. 755–759. doi: 10.1182/blood.2020007079.

Xia, X. (2021) 'Domains and Functions of Spike Protein in SARS-Cov-2 in the Context of Vaccine Design', *Viruses*, 13(1). doi: 10.3390/v13010109.

Xiao, J. *et al.* (2004) '[Glucocorticoid-induced diabetes in severe acute respiratory syndrome: the impact of high dosage and duration of methylprednisolone therapy]', *Zhonghua Nei Ke Za Zhi*, 43(3), pp. 179–182.

Yang, B. *et al.* (2020) 'Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Patients Who Received Compassionate-Use Leronlimab', *Clinical Infectious Diseases*, (ciaa1583). doi: 10.1093/cid/ciaa1583.

Zaki, A. M. *et al.* (2012) 'Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia', *The New England Journal of Medicine*, 367(19), pp. 1814–1820. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1056/NEJMoa1211721.

Zeng, Q.-L. *et al.* (2020) 'Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients With Coronavirus Disease 2019', *The Journal of Infectious Diseases*, 222(1), pp. 38–43. doi: 10.1093/infdis/jiaa228.

Zhu, N. *et al.* (2020) ‘A Novel Coronavirus from Patients with Pneumonia in China, 2019’, *The New England Journal of Medicine*, 382(8), pp. 727–733. doi: http://dx-doi-org.uaccess.univie.ac.at/10.1056/NEJMoa2001017.

Zimmer, C., Corum, J. and Wee, S.-L. (2021) ‘Coronavirus Vaccine Tracker: genetic vaccines’, *The New York Times*, 5 March. Available at: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html (Accessed: 7 March 2021).