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European legal issues stemming from the COVID-19 pandemic: regulatory, intellectual property, contract and competition law relevant to cell and gene therapy products

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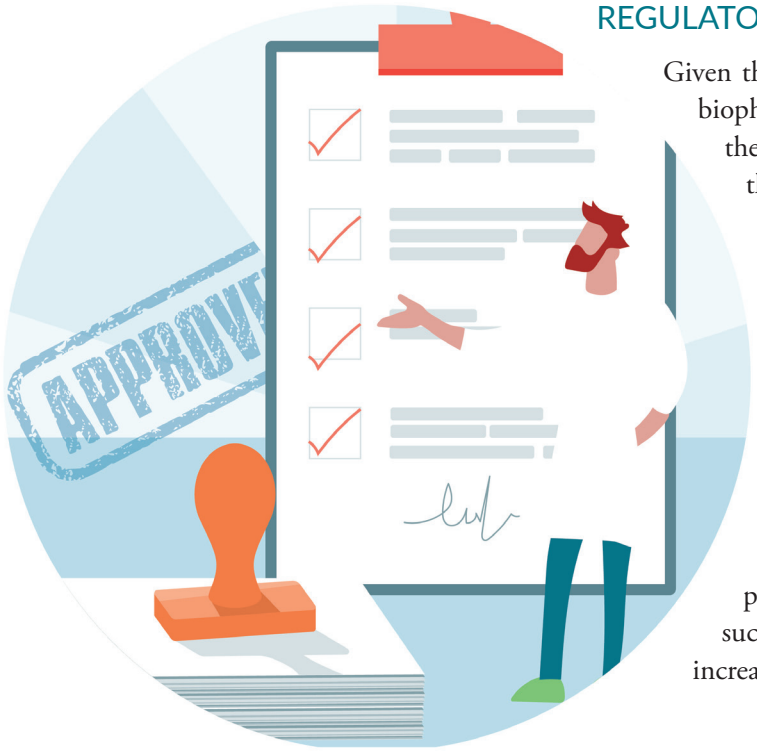
INTRODUCTION

On 30 January 2020, the Director-General of the World Health Organisation (WHO) declared the SARS-CoV-2 outbreak a public health emergency of international concern [1]. At the time, there were 98 reported cases in 18 countries outside China and no deaths outside China. By 11 March 2020, the WHO declared COVID-19 a global pandemic with 118,000 reported cases in 114 countries and over 4,000 deaths [2]. As at 14 January 2021, there were over 91 million global confirmed cases of COVID-19, including over 1.9 million deaths reported to the WHO [3]. The speed and impact of this pandemic has been unprecedented. In this article, we consider some of the legal challenges and considerations that have arisen during the COVID-19 pandemic, with a focus on Europe, and explore how this has impacted the biopharmaceutical industry in its drive to develop vaccines and treatments for COVID-19, with a particular emphasis on the impact to the cell and gene therapy industry.



REGULATORY & PROCEDURAL CHALLENGES

Given the broad nature of regulatory challenges for the biopharmaceutical industry as a whole stemming from the COVID-19 epidemic, this section focuses on the challenges specific to the cell and gene therapy industry. The regulatory environment surrounding advanced therapy medicinal products (ATMPs) is already complex, with a number of interlocking regulatory regimes, a complex global supply chain, and difficult reimbursement environment. There are also particular difficulties in conducting trials in small patient populations suffering from rare diseases. The combination of small patient populations and the ATMP regulatory environment already puts strain on the authorization and launch of such products; the COVID-19 pandemic has only increased these complications.

Clinical trials

ATMPs are often developed to treat small patient populations. This means that randomized controlled trials are difficult to run. Instead, small patient numbers are enrolled in clinical trials, which are often supplemented by post-marketing obligations and/or the collection of real world data. The treatments are also novel, developed to treat rare diseases, meaning a number of precautions are often built into the protocol to monitor unforeseen adverse reactions and ensure the safety of patients. Conducting such trials is already difficult, even without the additional stain of a global pandemic.

At the start of the pandemic, clinical trials in many countries were stopped. The Commission and EMA issued guidance for clinical-trial sponsors on how they should adjust the management of clinical trials during the pandemic to enable trials to continue [4]. For example, it may be necessary for the protocol to be amended to change recruitment practices or to include social distancing measures, quarantine and self-isolation requirements, or mHealth and telemedicine aspects could be incorporated to minimize travel or to reduce interactions between healthcare professionals and patients. While these difficulties have affected all clinical trials, the impact is arguably greater for trials involving small patient populations, spread across the globe, which is often the case for certain ATMP trials. Further, many of the patients involved in ATMP trials may be vulnerable or have been told to shield during the pandemic, meaning their willingness to be part of a clinical trial may have changed.

Logistical difficulties and delays with clinical trials also put a strain on the marketing authorization process for ATMPs. Given the small patient numbers that are involved in many ATMP trials, there had already been pre-pandemic discussions among authorities on the level of data that is required for authorization of these products, and the extent to which gaps in the data can be supplemented post-marketing. Further delays in clinical trials, and reduced numbers of subjects due to COVID may exacerbate these data difficulties and lead to further delays in marketing authorization.

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However, the pandemic has also led to innovation in clinical trials, particularly in the use of digital technologies during clinical trials, and in authorities accepting real world data as part of regulatory submissions. The routine use of mHealth technologies has helped to streamline trials, and in fact increased efficiencies with patient recruitment and communication [5]. Such technologies could also assist with data collection, including of additional supporting data, such as quality of life data that are needed for reimbursement discussions. This could be a welcome unintended consequence of speeding up the adoption of remote monitoring technologies in clinical trials. Similarly, there have been global collaborations on the collection of real world pharmacovigilance data associated with COVID vaccine use [6], and it is hoped that such initiatives will increase the authorities' comfort with accepting such data.

Manufacturing

Certain ATMPs (particularly autologous cell therapies) are manufactured at multiple sites, starting with samples collected from the patient. Further, despite the EU-wide nature of the authorization of such products, the manufacturing processes are still controlled at the national level; where materials travel through a number of countries, different rules in relation to licensing or customs apply.

Transport of people and goods has obviously been impacted over the last months, and while there can be exemptions for treatment, these are not uniformly applied. Similarly, national differences in terms of lockdown, quarantine and travel restrictions causes complications for global products such as these. The manufacturing chain for ATMPs is usually time critical, and so minor delays at customs or due to travel restrictions may lead to samples being unusable or products being spoiled. The EMA has provided guidance [7] to authorization holders on flexibilities that can be introduced to the manufacturing supply chain to ensure continued supply of medicines during the pandemic, for example to ensure the continued validity of good manufacturing practice certificates, and flexibilities around inspections. This guidance also applies to ATMPs.

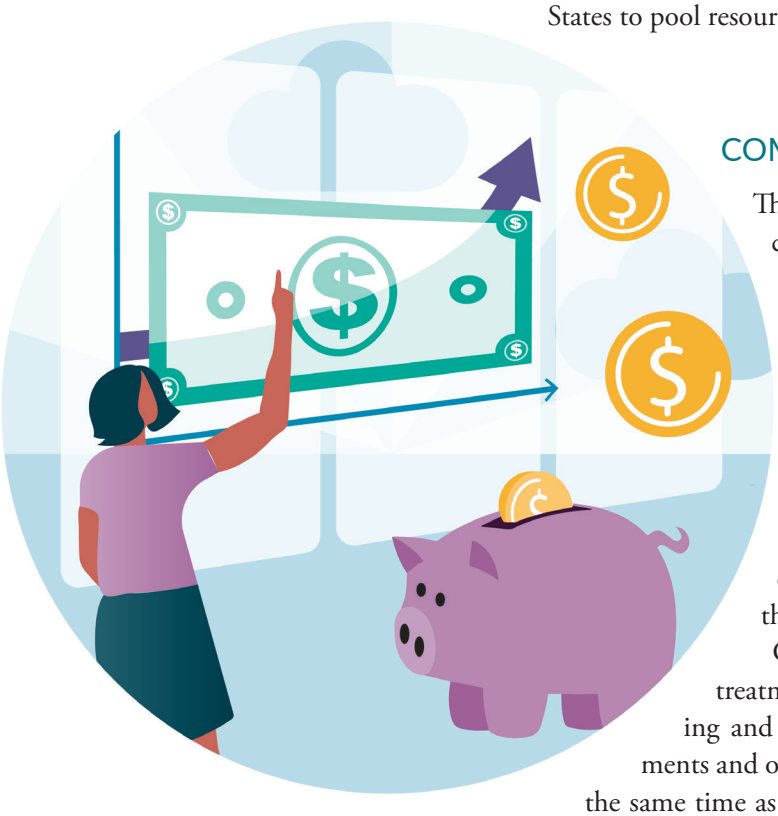
The urgency of the pandemic has shown that quick legislative changes are possible in order to streamline the process across the EU and minimize national differences. While not relating to manufacturing specifically, new legislation has been introduced to facilitate the conduct of clinical trials using products containing or consisting of genetically modified organisms [8]. This is specifically focused on development of vaccines and therapies to treat COVID-19, but demonstrates that rapid changes can be made to streamline the process across the EU. These harmonization measures may expand beyond COVID-19 therapies and address some of the difficulties identified here.

Pricing & reimbursement

Pricing and reimbursement for specialized products has always been difficult. These products are often used to treat a small number of patients at high cost, and healthcare systems have been reluctant to purchase them without large discounts. The pandemic has exacerbated this, as healthcare systems have had to make difficult decisions on prioritizing treatment and allocation of finite resources.

However, the pandemic has increased the use of centralized procurement regimes, whereby the European Commission on behalf of member states (and other countries which are signatories to the Joint Procurement Agreement) has sought to pool buying power. Completed

joint procurements cover PPE, testing kits, as well as vaccines and Gilead's remdesivir. Other planned procurements are intended to cover ICU medicines, vaccine carriers, waste containers, injecting devices, more personal protective equipment (PPE) as well as anesthetic consumables [9]. Centralized procurement is specifically encouraged where serious cross-border threats to public health are involved, which is clearly the case here, but the use of such systems will hopefully encourage authorities to further utilize voluntary agreements between Member States to pool resources and ensure quick access to ATMPs.



COMMERCIAL TRANSACTIONS

The COVID-19 pandemic has led to accelerated commercial transactions and new contracting models for those companies developing vaccines and products to treat COVID-19 patients. Whilst vaccines are not classified as ATMPs, some of the vaccines in development involve gene-based technologies, and the transactions highlight what can be achieved contractually in the development of new pharmaceutical products and vaccines, or in the redeployment of existing products for other purposes when there is sufficient political and societal pressure.

Companies involved in developing COVID-19 treatments have found themselves negotiating funding and supply agreements to enable multiple governments and other organizations to purchase their products, at the same time as developing the products and ramping up their supply chains, all under intense public scrutiny [10,11].

In addition to logistical issues surrounding the sheer volume of contracts required, there have been difficult discussions with payers about who should bear the risk of product liability claims brought by patients who may have been injured as a result of the new products. Companies placed under pressure to develop their new products at speed and then roll them out to millions or even billions of patients have been extremely sensitive to this potentially enormous downstream risk, and many have asked governments to share in the risk of product liability claims.

This discussion has been relatively straightforward in the US, where the 2005 Public Readiness and Emergency Preparedness Act (PREP Act) offers immunity from tort claims for product liability for products supplied in a public health crisis. For developing and least developed nations, the COVAX vaccine scheme co-led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO is setting up a compensation fund for individuals who might suffer any side-effects from COVID-19 vaccines [12,13].

The position in the EU is less clear cut than in the US. This prompted Vaccines Europe, a division of the European Federation of Pharmaceutical Industries and Associations (EFPIA), to engage with the EU and governments around the introduction of no-fault and non-adversarial compensation systems, and exemptions from civil liability for vaccine developers during the pandemic [14,15]. For now, the Commission is addressing liability with individual manufacturers via the relevant supply agreements on a case by case basis (see, for instance the European Commission's press release regarding its contract with AstraZeneca, which states

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that the Member States will indemnify the manufacturer for liabilities incurred under certain conditions, while liability still remains with the companies [16]).

Designers and manufacturers of ventilators experienced similar issues following requests to scale up and manufacture products to treat COVID-19 patients at the start of the pandemic. In the UK, the government responded by agreeing to indemnify designers and manufacturers of rapidly manufactured ventilator systems not only for product liability claims, but also for infringement of third-party intellectual property (IP) rights, accepting that, as a result of the accelerated process, there was less time to consider the patent and design rights landscape and design-around, license-in, or seek to invalidate third party IP rights [17].

COMPETITION & COLLABORATIONS

Since the start of the COVID-19 pandemic, we have witnessed significant collaborations between companies and institutions engaged in the development of vaccines and therapies to treat COVID-19. Such collaborations, including for the development of vaccines using gene-based technologies, frequently have involved cooperation between competitors and thus must be structured carefully.

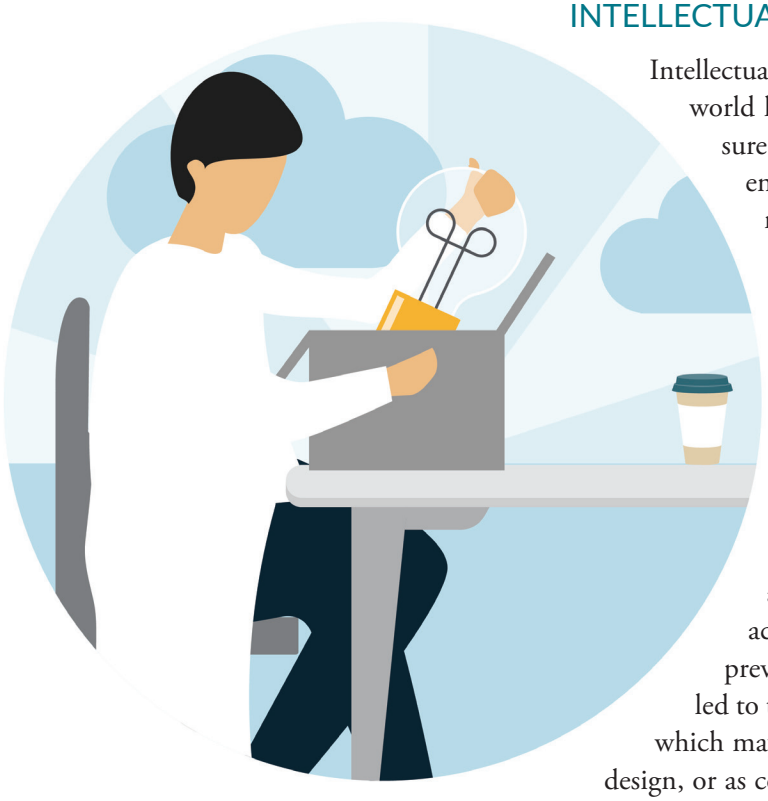
In the early part of the COVID-19 pandemic, the UK's Competition and Markets Authority, the European Commission as well as national competition authorities in other countries responded to growing demands from businesses to provide guidance for parameters of lawful cooperation among competitors seeking to address the challenges posed by the epidemic.

Competition laws generally restrict information exchange and supply chain optimization agreements between competitors. However, a real crisis such as COVID-19, clearly creates an imperative to permit and even encourage such exchanges and agreements. The authorities' guidance sets out areas of permissible cooperation but also the limits of such cooperation. This is particularly relevant for the pharmaceutical sector, where companies are often jointly developing vaccines, tests and therapies, and for those manufacturing and distributing medical devices.

The limits set out in the guidance broadly seeks to ensure that any cooperation is strictly necessary, limited to the duration of the pandemic, that it is proportionate and specifically benefits customers/patients. In addition, the UK government adopted specific orders excluding the application of UK (but not EU) competition laws to certain qualifying activities in the provision of health services to the NHS in England and Wales, again subject to certain requirements and limitations.

The key takeaway is that competition law will continue to be relevant to any form or co-operation between actual or potential competitors and that there is no blanket exclusion or relaxation of competition laws that will obviate the need for specific advice.

INTELLECTUAL PROPERTY



Intellectual property offices and courts across the world have implemented multiple measures to ensure, as far as possible, that the protection and enforcement of intellectual property rights is not adversely affected by lock-downs and the need to work remotely as a result of the COVID-19 pandemic. This has included the extension of deadlines for filing evidence and submissions before registries, the ability to file documents digitally, as well as virtual registry hearings, court hearings and trials.

The COVID-19 pandemic has led to an unprecedented global effort in accelerated research and development efforts across academia and industry to diagnose, treat and prevent infections. These efforts have inevitably led to the creation of intellectual property, some of which may be potentially protectable as a patent, as a design, or as copyright or may be treated as a trade secret. This has, in turn, led to debates as to the extent to which the owners of such IP should seek to protect and enforce their rights. The outcome of this debate may impact the IP position for companies in the cell and gene therapy space, especially as some of the vaccines being developed deploy gene-based technologies.

On 1 June 2020, the WHO called key stakeholders and the global community to commit to take action to, amongst other things:

- Promote innovation and facilitate the sharing of intellectual property for COVID-19 detection, prevention, treatment and response;
- Promote that all COVID-19 publicly-funded and donor-funded research health product outcomes include non-exclusive voluntary licensing and the sharing of IP rights; and
- Encourage that all research outcomes are published under open licenses that allow access free of charge, use, adaptation and redistribution by others with no or limited restrictions [18].

The WHO also called on IP rights holders to voluntarily license their rights on a non-exclusive and global basis, to share relevant knowledge, IP and data to enable widescale and worldwide production and distribution, including by placing it in the WHO COVID-19 Technology Access Pool (C-Tap) [19]. It is notable that of the 40 countries that have, to date, endorsed the WHO solidarity call to action, the majority are developing countries.

On 2 October 2020, India and South Africa sent a proposal to the World Trade Organisation (WTO) requesting a waiver from the implementation, application and enforcement of a number of provisions of The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS; TRIPS is an international agreement that applies basic in international trade principles regarding IP) until widespread vaccination is in place globally and the majority of the world's population has developed immunity. So far, the proposal has been rejected by the majority of WTO members, including the UK Government, which stated that such an

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"extreme measure to address an unproven problem" would be "counterproductive and would undermine a regime that offers solutions to the issues at hand" [20]. It pointed to existing mechanisms that facilitate the sharing of IP, including the initiatives being developed by the WHO. The proposal is due to come before the WTO Council formally in December 2020.

If a waiver to TRIPS is agreed, biopharmaceutical companies would likely lose some of the protection afforded to them through their ability to control the use of their IP rights. Although the TRIPS waiver proposal is not limited to developing and least developed countries, we anticipate that, if a waiver is agreed, its application is more likely to be limited to such countries. Even if a waiver is not agreed, WTO countries are entitled under TRIPS to allow the use of the subject matter of a patent without the owner's consent in the case of a national emergency or other circumstances of extreme urgency [21].

Even if the TRIPS waiver is not deployed, where there is a national security risk, emergency and/or a public interest need, many countries have specific provisions in their patents laws that provide either a defense to patent infringement, authorize certain acts to be done which might otherwise constitute patent infringement or which enable IP rights to be expropriated from their owners. The UK Patents Act 1977, for example, includes "Crown Use" provisions whereby a government department can authorize the infringement of a patent without the owner's consent to provide services to the Crown and such Crown use includes the production or supply of specific drugs and medicines [22]. Although there was an amount of speculation and hype early on in the pandemic as to whether governments would deploy these emergency measures, we have instead seen a significant amount of commercial deals being struck between governments and companies developing vaccines and therapies to treat COVID-19.

FINAL REMARKS

This article only addresses some of the legal challenges presented by the COVID-19 pandemic and how they may impact cell and gene therapies. At the time of writing, the outlook is looking favorable for at least three of the COVID-19 vaccines in development. The speed of development of numerous COVID-19 vaccines in under 12 months is unparalleled. This has, at least in part, been possible due to flexibility and revised guidance from regulatory authorities, the implementation of emergency legislation, as well as innovative ways of contracting and collaborating between academics, governments and the biopharmaceutical industry. In contrast, research and development efforts for non COVID related cell and gene therapies have been more challenging this year, with companies experiencing delays to clinical trials and caution from investors. Nevertheless, the fact that a number of the COVID-19 vaccines in development deploy gene-based techniques may assist in the long-term by helping to carve a path to market and also increase societal acceptance of such products.

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