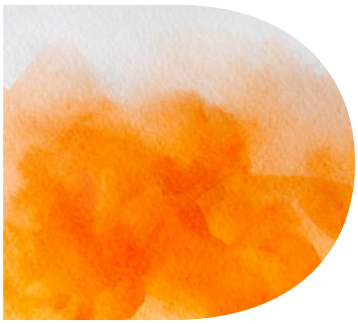
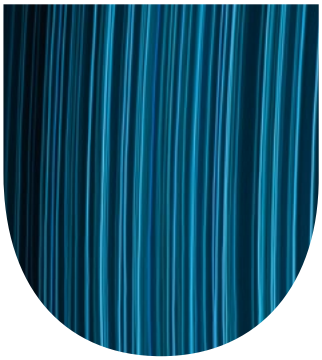
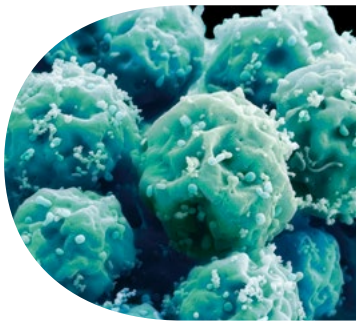
Bristows

Biotech Review of the Year

Issue 8







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*An analysis by **BIA and Radnor Capital Partners** reveals the strong performance of the UK-quoted biotech sector in 2020: 24 new American and 16 new European finance houses invested in the UK biotech sector for the first time, showing global recognition for UK innovation.*

Biotech is in for a rollercoaster 2021

Dear readers,

It would have likely been impossible, and certainly incomplete, to write this year's *Biotech Review* without devoting significant space to COVID-19. Be it investment patterns or research activity, the pandemic has touched every element of the global biotech market and will continue to do so in the months ahead. In truth, however, the pandemic is not the only notable trend of 2020 that could leave a lasting mark on the sector. Rather, from COVID-19 to heightened consciousness, collaboration and customisability, the biotech sector is set for a rollercoaster 2021.

Alongside COVID-19, a hallmark of 2020 has been heightened public 'consciousness'. True, healthcare services are often popular media fodder, but the pandemic has shone a light onto some of the more overlooked aspects of the sector. Never has there been such intense public interest in how vaccines are produced, for example. Nor has the approval process for medicines been so widely discussed. What's more, according to Google's analytics, searches for 'Biotech' more than doubled between June and July alone. In short, biotech is now firmly front of mind for many, but, as we discuss in this year's *Biotech Review*, whether this will affect investment activity in the years to come remains the million-dollar question.

From consciousness we move to collaboration, a keynote of last year and likely a defining feature for 2021. Though collaboration has always been the lifeblood of the sector, the race to develop a vaccine has seen a notable intensification in cooperation between biotech companies, research institutions and governments. The recently-launched Oxford-AstraZeneca vaccine - which was rolled out after swift multi-country trials and after the commendable efforts of Oxford's Jenner Institute, Italy's Advent Srl, the US' IQVIA, and the British-Swedish AstraZeneca - is emblematic in this regard. And, just as with heightened public consciousness, it remains to be seen whether the increased collaboration of the last few months will leave an indelible mark on the sector – a central question for a number of our articles this year.

Looking ahead, one thing we can predict with confidence is a significant growth in customisable, personalised medicine. Gene and cell therapies are already moving from theory to reality, with the FDA publicly declaring it expects to be approving ten to twenty cell or gene therapy products a year by 2025. In the months ahead, we will likely see not only further development of such technologies, but significant investment activity also.

In short, 2021 is an exciting time to be working in the biotech sector. As a firm, we have seen our clients, who occupy every corner of the market, not just grow, but complete vital work at an incredibly difficult time. It is these observations that have shaped the pages of the *Biotech Review* – covering everything from the rise of AI through to transgenic mice and the Medicines and Medical Devices Bill – which we are delighted to share with you.

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Will Private Equity make waves in the life sciences sector in 2021?

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Private equity has, arguably, long been seen as something of an outsider to the Life Sciences sector. Until recently, activity tended to focus on more traditional healthcare and infrastructure sectors, where revenue streams are established.

But in 2021, could the tide change?

A new niche for a traditional model?

In truth, the tide has already turned. Recently we have seen a significant expansion of Private Equity activity in the wider Life Sciences sector, not least in subsectors once considered the realm of more specialist investors. From services to generics, Private Equity can see greater value in the broader Life Sciences sector, with positive ripple effects for investors and innovators alike. What we will likely see in 2021 is not the breaking of entirely new ground, but the continuation of a swell that is already reshaping the market.

The key barrier for Private Equity investing in the Life Sciences sector has typically been the long timescales and unpredictable revenue streams from an innovation or spin-out to a product finally reaching the market and generating stable income streams. For example, while the potential gains from a successful therapeutic reaching the market might be huge, the risks in the years between investment and result are also significant. The apparent complexity of the market, too, has often acted as a barrier to investor activity.

From generics, to medtech, diagnostics, pain management or the aforementioned wider services, the Life Science sector offers a multitude of options that fit the traditional investment model once past the early investment stages. New pools of money are flowing into the sector in these tiers of development, where valuations based on sales provide the financials that private equity is looking for.

A typical example of this occurred in January 2020, when Synova Capital invested in Charnwood Molecular, a leading UK provider of outsourced drug discovery services. As a services provider, Charnwood's client base promised a regular revenue stream with which to meet any payments due to acquisition financing, allowing Synova to follow the traditional route of increasing the value of its investment before selling it on without concerns over long timescales or binary pass/fail product approval risks.

Turning tides generate some froth

In addition to the increasing awareness of these opportunities, we see a greater appetite for risk amongst investors, perhaps helping overcome the historic reticence to invest in a sector where specialist knowledge is a prerequisite. This 'frothy' mood resembles the excitement in 2007 and 2008, albeit thankfully without the quick sales, overleveraging and discounting of risk that characterised the instability of the time.

Indeed, the greater appetite we are seeing amongst private equity investors is typical of a healthy investment ecosystem. Deals for generic sales or service streams allow pharmaceutical companies to clear older assets from the books, providing increased capital to invest in innovation, whether in-house or through their investment arms.

This 'recycling' of assets also suits established strategic investors in the sector, who see no competition with Private Equity in the early stages of investment, but benefit from the increased innovation that private equity houses are, in essence, funding.

This trend pre-dates the pandemic and has not been adversely affected by the economic disruption that characterised 2020. Rather, there has been an increased awareness of the opportunities.

Long term trends bode well

In June 2019, months before the coronavirus surfaced, European midmarket private equity group Duke Street acquired Kent Pharmaceuticals and Athlone Laboratories, manufacturers of specialist off patent/generic pharmaceuticals, from pharmaceutical company DCC Vital. Kent's established sales channels to hospitals and pharmacy wholesalers provided a revenue stream and sales-based valuation that fit the private equity investment criteria, Kent and Athlone gained a new backer, and DCC received a capital injection to invest in new early-stage companies and products.

*Investor activity more broadly continues to be strong. In the first quarter of 2020, eight biotechs alone raised $1.3bn. By the end of 2020, **71 biotech companies** had gone public, with 13 of them raising more than $250m each. The biotech sector enters 2021 from a position of strength.*

The continued market success of the life sciences sector, combined with higher levels of public interest owing to the pandemic, bodes well for the market in 2021. Increased investment is rarely a bad thing, and interest from Private Equity in later-stage companies is providing exciting new capital to fund greater innovation in the future.

As ever, the success of the sector rests in the hands of its astute academics, savvy financiers and expert professionals; the influx of private equity only adds new minds to this already potent mix.

Other PE Transactions in 2020: PE Seller and PE Buyer

- Apollo purchased speciality pharma company Covis from Cerberus for a price reported to be in excess of $700M
- Permira acquired a controlling stake in Neuraxpharm from Apax for $1.9 Bn

Covid put on hold the reported sale of Curium by CapVest for up to $3bn to a variety of PE houses (including Nordic Capital, Bain and CVC).

Collaboration: Sustainable future or dangerous pathway?

One of the unexpected positives arising from the COVID-19 pandemic has been the number of collaborations between competing firms aimed at delivering benefits to consumers.

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Associate

Such arrangements can help to overcome shortages of essential products and fix supply chain disruptions, reducing the need for state intervention or other costly remedies. In the pharma sector, competitor collaborations can enable firms to pool expertise and resources in the research and development of new vaccines and treatments, facilitating the development of products that no single firm could achieve. Pharma companies around the world have indeed entered into many such collaborations in the fight against COVID-19. In the area of plasma-based therapies alone, we have seen the creation of the CoVIg-19 Plasma Alliance[1]; Grifols' collaboration with various US public health agencies[2]; Emergent BioSolutions' partnership with BARDA[3]; a partnership between Kamada and Kedrion Biopharma[4]; and Sorrento Therapeutics' collaboration with Mount Sinai Health Systems.[5]

Whilst competitor collaborations can create significant benefits for consumers (and not just in the context of a response to a global threat as significant as the pandemic), they also have the potential to give rise to competition law issues. Without appropriate safeguards, they can reduce firms' incentives and ability to compete, increase the likelihood of collusive outcomes, and in extreme cases may even put non-participating competitors at a disadvantage, leading to market foreclosure. Businesses therefore need to pay careful attention to general competition law principles and agency guidance when collaborating, or risk facing enforcement action. Measures such as limiting the collaboration in time and scope, and keeping the exchange of commercially sensitive information to a minimum, can help to reduce the competition law risks.

1 https://www.fiercepharma.com/manufacturing/takeda-led-alliance-starts-manufacturing-covid-19-plasma-therapy-as-phase-3-kicks-off

2 https://www.grifols.com/en/view-news/-/news/grifols-announces-formal-collaboration-with-us-government-to-produce-the-first-treatment-specifically-targeting-covid-19

3 https://investors.emergentbiosolutions.com/news-releases/news-release-details/emergent-biosolutions-joins-us-governments-warp-speed-program

4 https://www.kamada.com/news/kamada-and-kedrion-biopharma-announce-global-collaboration-for-the-development-manufacturing-and-distribution-of-a-plasma-derived-anti-sars-cov-2-covid-19-polyclonal-immunoglobulin-product/

5 https://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-and-mount-sinai-health-system-jointly-develop-covi

The role of competition authorities

The severe consequences of breaching competition law can sometimes have a chilling effect on firms considering engaging in collaborative action. To mitigate this chilling effect and increase legal certainty, several competition authorities have issued guidance on how firms can cooperate to address the effects of the COVID-19 crisis without falling foul of the competition rules. In March 2020, for instance, the US Federal Trade Commission (FTC) and the Department of Justice (DOJ) published a Joint Antitrust Statement Regarding COVID-19[6]. The European Commission's Temporary Framework[7] for assessing antitrust issues arising from Covid-related business cooperation followed shortly afterwards. In issuing such guidance, authorities sought to strike a careful balance between giving firms the necessary leeway to address market disruptions and ensuring that firms do not use the crisis as an excuse to engage in anti-competitive conduct.

While giving a positive message to the market, general guidance may fail to provide the necessary assurance in less clear-cut cases – and may therefore be insufficient to reduce the risk of a chilling effect. In such cases, more specific guidance may be required. Recognising the urgency of certain situations relating to the pandemic, a number of authorities have put in place mechanisms for speedy and specific ad hoc guidance, in the form of comfort letters or similar tools. In April 2020, for example, the European Commission issued a comfort letter[8] to Medicines for Europe (formerly the European Generics Medicines Association), confirming that "*in the present exceptional circumstances*" the proposed cooperation between pharma suppliers targeting shortages of critical medicines would not raise concerns under the EU competition rules. In the US, firms seeking to collaborate in response to the pandemic can now request an expedited response to a Business Review Letter. In their Joint Antitrust Statement, the FTC and DOJ said they would aim to "*respond expeditiously to all COVID-19-related requests, and to resolve those addressing public health and safety within seven calendar days of receiving all necessary information*".

The global nature of many Covid-related competitor collaborations in the pharma sector has also called for close cooperation between competition authorities. If agencies were to fail to take a joined-up approach to examining pharma collaborations of global scope and to reach radically different views on the competition risks they present, then many such collaborations would struggle to get off the ground. It may be trite to say that COVID-19 knows no borders, but the reality is that the kinds of collaboration needed to address some of the challenges raised were truly international in scope, requiring international agency responses. More broadly, international cooperation between agencies facilitates the exchange of experiences and best practices in dealing with competitor collaborations. In this regard, the UK Competition & Markets Authority's recent statement in its draft Annual Plan[9] for 2021/22 that it will "*continue [its] close engagement and cooperation with other competition and consumer agencies in the EU and globally*" is to be welcomed.

Looking to the future

Competition authorities around the world have demonstrated their ability to act quickly and responsibly in helping firms respond to the pandemic. As we begin to look beyond the present crisis, it is worth considering whether the actions taken by authorities in the last year might provide a template for promoting other forms of welfare-enhancing competitor collaboration. One issue that springs to mind in this context is the climate crisis. The EU's 'Green Deal' emphasised the need for a "*modern, resource-effective and competitive economy*" to address the challenge of climate

6 https://www.justice.gov/atr/joint-antitrust-statement-regarding-COVID-19

7 https://ec.europa.eu/info/sites/info/files/framework_communication_antitrust_issues_related_to_cooperation_between_competitors_in_COVID-19.pdf

8 https://ec.europa.eu/competition/antitrust/medicines_for_europe_comfort_letter.pdf

9 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/944608/AnnualPLAN__-.pdf

change[10], and it is now more important than ever that businesses can cooperate and innovate for the benefit of the environment. Agreements between competitors to develop and adhere to high environmental standards, or information-sharing mechanisms to reduce environmental impacts, should not founder for fear of infringing the competition rules.

In Europe, the Commission has recognised in the context of the pandemic that competition law self-assessment often fails to provide sufficient legal certainty for businesses seeking to collaborate with competitors to develop innovative solutions. The Commission's resuscitation of the comfort letter procedure could signal a welcome return to a more positive approach to offering competition law certainty. While the resource-intensive nature of the procedure should not be underplayed, there is nonetheless a case for extending it beyond the current crisis to give businesses a means of protecting themselves before implementing particularly novel or far-reaching initiatives.

At the very least, more concrete guidance is needed from the Commission and other competition authorities on how they will treat arrangements that are put in place for environmental or sustainability purposes. The urgency of the climate crisis calls for more detailed guidance on how the wider social benefits of competitor collaborations will be assessed, including detail on the kind of evidence that can be adduced to demonstrate the net benefits of an initiative. In 2019 the Commission began a review of its Horizontal Cooperation Guidelines and the block exemptions currently in place for research and development and specialisation agreements.[11] This is an ideal opportunity for a root-and-branch review of the current legal framework for competitor collaborations.

10 See https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en

11 See https://ec.europa.eu/competition/consultations/2019_hbers/index_en.html

Will the new pharmaceutical strategy for Europe bring changes to the biopharmaceutical rewards system?

Amidst the pandemic and negotiations to avoid the UK crashing out of the EU without a deal, the European Commission (EC) had time to release its (bio)pharmaceutical strategy for Europe[1] towards the end of 2020.

Xisca Borrás
Of Counsel

The EC strategy revolves around fulfilling unmet medical needs and ensuring accessibility and affordability of medicines, supporting a competitive and innovative European pharmaceutical industry, and securing the supply of medicines across the EU to avoid shortages.

Of course, the importance of fulfilling each and every one of these objectives has been made clear by the COVID-19 crisis. Ultimately, the pandemic has exposed not just the EU's dependence on critical innovations and technologies, but also the frailty of supply chains.

The release of the strategy document coincided with the issuing of another equally relevant communication from the EC: an intellectual property (IP) action plan *"to support the EU's recovery and resilience"*[2]. Both documents point towards changes in the incentives system. This is not new, as the EC has been reviewing the incentives system since 2016 and the introduction of the SPC manufacturing waiver was the (first) outcome of the review.

More tailored incentives for treatments of unmet medical needs?

In the strategy document, the EC echoes the need to rethink policies to stimulate innovation, in particular in areas of unmet needs. For this reason, the EC strategy proposes to revise the legislation on medicines for children and rare diseases to improve the therapeutic landscape and address unmet needs, like paediatric cancer, through more tailored incentives.

This fits into the EC's broader proposal to review the system of incentives, possibly including a greater 'conditionality' of incentives to support broader access for patients, which the EC considered to be hindered by a lack of transparency of research costs or return on investment.

1 https://eur-lex.europa.eu/legal-content/EN/TXT PDF/?uri=CELEX:52020DC0761&from=EN

2 https://ec.europa.eu/docsroom/documents/43845

This position follows from the EC joint evaluation of the published last summer[3], which took place in the framework of the broader pharmaceutical incentives review that the EC has been carrying out since 2016. The resultant report found that while the Orphan and Paediatric Regulations have fostered the development and availability of medicines for patients with rare diseases and for children, the development has been boosted mainly in areas where adult development was already planned. In this regard, the evaluation found that the Paediatric Regulation seems to work best in areas where the needs of adult and paediatric patients overlap.

The reason being that, despite the obligations under Paediatric Regulation to develop new medicines in children, there is no dedicated instrument to direct development in areas relevant for children, meaning that the development of new medicines for children therefore remains mainly driven by adults' needs.

On the rewards and incentives of the two pieces of legislation, the report criticised the 10 year orphan market exclusivity for not being fully justified for certain orphan medicines for some rare diseases, in cases where the market has started to look more similar to 'standard' medicines. The evaluation refers to them as 'often well-established use products, or medicines authorised for multiple orphan conditions.'

According to the report, the rewards in the Paediatric Regulation seem to partially compensate the cost of conducting the Paediatric Investigation Plan and so it is partly fulfilling its role, but it has not shown to be effective in stimulating the development of medicines whose development for adults is not attractive. Obtaining this reward may be complex, as companies have to request it individually at the various national patent offices. Having said that, the report concluded that the incentives and rewards provided by both regulations come with a cost, but the benefits the legislation brought for children appear to outweigh the costs imposed on both industry and society.

So, judging by the contents of last summer's report, the review of the legislation on medicines for children and rare diseases to improve the therapeutic landscape and address unmet needs, as announced in the EC's strategy document, may try to exclude orphan market exclusivity from those products that receive an overcompensation as a result of the protection.

A less fragmented IP system?

On its part, the EC's IP action plan has identified the fragmentation of the EU's IP system as one of the main challenges in the upgrading of the EU's IP framework. For this reason, the EC fully supports the unitary patent and the system of centralised litigation before the new Unified Patent Court (assuming this eventually comes into effect). The EC has high hopes for the unitary patent system, considered 'a key tool for the EU's industrial recovery, especially for the renewable energy, electronics, aerospace and defence, and mobility ecosystems.'

In similar lines, the IP action plan highlights that the SPC system suffers from fragmented implementation across Member States, which translates into inefficiencies and a lack of transparency and predictability. For this reason, the EC is assessing ways to address these pitfalls, including the possibility to introduce a unified SPC grant mechanism and/or create a unitary SPC title.

Another example of the fragmented IP system is the Bolar exemption. The way in which Member States have transposed article 10.6 of Directive 2001/83/EC on medicinal products for human use into national law is far from harmonised, as the Directive only provides for minimum standards. While in some countries the Bolar exemption is limited to activities related to the generation of data for regulatory submissions of generic submissions in the EU/

3 https://ec.europa.eu/health/human-use/paediatric-medicines/evaluation_en

EEA, in other countries it includes activities related to the generation of data for any type of submission, including full applications, for regulatory approvals outside of the EU/EEA. The EC hints at a review of the Bolar provision, to support greater generic and biosimilar marketing authorisation applications to increase competition.

What does the future hold?

Amongst many other initiatives, the EC proposes to revise the legislation on medicines for children and rare diseases to improve the therapeutic landscape and address unmet needs through more tailored incentives in 2022, including exploring new types of incentives for innovative antimicrobials. At the same time, the EC also proposes revising the system of incentives and obligations in the pharmaceutical legislation, taking into account the relationship with IP rights, to address market competition considerations and improve access to generic and biosimilar medicines, including the Bolar exemption, in 2022.

The EC's proposals are many and very ambitious, so the involvement of diverse and engaged stakeholders is needed more than ever to make the most of the opportunity to improve the competitiveness and attractiveness of the EU to attract a strong, fair and competitive industry.

*Public interest in the biotech sector has arguably never been greater. Though this is no small part down to COVID-19 - in January 2020 alone, 'Coronavirus' appeared in 19,000 newspaper headlines across the world - there has been a significant increase in interest in biotech. In fact, **Google searches** for the word 'Biotech' doubled between June and July 2020 alone. More eyes are trained on the sector than ever before.*

Q&A: What does 2021 hold? The industry view

How has the industry reacted to the tumultuous year gone by, and what does the future hold?

To hear first hand how the sector has reacted to the year gone by, and how it feels about the year ahead, we caught up with **Mark Duckworth**, Senior Director, Legal Services at European specialist pharmaceuticals company **Norgine**:

Founded in 1906, **Norgine** is one of the leading pharmaceutical companies, developing, manufacturing and commercialising products in every major European market.

What are the main issues that you have been dealing with in 2020 that will impact the next 12 months?

Clearly, the biggest issue brought about by the pandemic has been adapting to new ways of working. Remote working for all office based staff is now embedded and we've found it has operated well. We have continued to see good levels of efficiency and effectiveness and have leveraged our IT capability to ensure effective working and continued communication. We need to ensure that our staff can continue to work effectively within the myriad restrictions around Europe and ensure that we are resilient and supportive of one another, taking into account every individual's different personal circumstances.

In terms of production, we already had extremely high standards in our production facilities, so we have been able to make adaptions to that to enable us to continue production safely and at pre-COVID-19 levels. We shouldn't, of course, forget Brexit, and we have ensured that we are as thoroughly prepared as we possibly can be – bearing in mind we need to ensure continuity of supply to our patients who depend on our medicines. Patients are at the centre of everything we do.

Do you feel anything has changed for good in the industry? What has Norgine learned from the pandemic disruption?

It is difficult to see any silver linings in the face of a global pandemic that has taken so many lives and caused so much pain, suffering and grief worldwide. However, I think that we have become more aware and tolerant of everyone's individual needs and challenges, and as a business I think we have embraced that and embedded a heightened level of understanding, care and concern within our culture.

Have you seen more collaborations between companies that wouldn't normally be open to cooperating?

It's clear that more collaboration has been happening within the Biotech and Pharma sectors and, while personally I've not seen a significant change, I know our business development colleagues have seen a sustained level of interest in collaborations of all kinds across the industry.

What trends do you expect for the market in 2021?

I think the only thing we can say with certainty is to expect the unexpected! It's clear that there will be winners and losers, but, as yet, I think it's difficult to say how the year will pan out. As vaccines take hold and economies recover, I do expect there to be some realignments and a bounce-back of corporate activity to look forward to.

The modern space race: Vaccine rollout and the regulatory regime

Greg Bacon
Partner

Xisca Borrás
Of Counsel

We might say that the last few months of 2020 bore witness to the 21st century equivalent of the space race. Across the world, biopharmaceutical companies have been racing to safely launch a COVID-19 vaccine, with the eyes of the media carefully following every twist and turn.

Humanity has not been slow to embrace the vaccine story: millions of pounds have been invested; millions of hours of research have been conducted; millions of words written; and millions around the world have eagerly awaited a successful outcome. Where, 12 months ago, vaccine technology would seldom prick the public consciousness, it has now become front page news. And whilst mRNA might not be as easy as 123, it has overtaken ABC and others to become one of the acronyms of the year, whilst interest in the vaccine approval process has never been greater.

Crucially, though, the rollout of the COVID-19 vaccine could provide a useful precedent for how future vaccines, not least novel nucleic or viral vector varieties, can be swiftly brought to market at a time of acute public need.

From Jenner to Pfizer: what is a vaccine?

Vaccines work by taking advantage of the body's immune system, and its exquisite ability (when working properly) to distinguish between friend and foe, and remember those foes it has previously seen. Vaccines expose the body to the invading pathogen so that the body then produces antibodies to the foreign material in a 'safe' environment, in the sense that the pathogen is presented in such a way that it is unable to infect the individual.

After inoculation with a vaccine, the development of antibodies primes the body so that when it is exposed subsequently to the invading pathogen, the immune response is significantly amplified, allowing the body to fight off the pathogen without deleterious consequences.

Further, mass vaccination protects populations as a whole, as it reduces the pool of susceptible individuals who are then able to re-transmit the infecting agent. In the most successful cases, vaccination can lead to complete eradication of the disease, as has heroically been achieved with smallpox.

Coronavirus disease 2019 (COVID-19) is, as its name suggests, caused by a virus, namely SARS-CoV-2. Vaccines against a virus have typically involved presenting to the body either the whole virus or subunit pieces of the virus (often fragments of protein), to trigger an immune response. There are four different routes for presenting the foreign viral material to the immune system that are generally used and have been investigated with COVID-19.

Where the whole virus is issued, steps are taken to prevent the virus infecting the host. This involves either a live attenuated form, using a weakened form of the virus, or an inactivated virus, wherein genetic material of

the virus has been removed/destroyed so as to prevent it from replicating in the body. In both cases, large amounts of virus are produced in the lab (which can be a disadvantage of this route given the risk of an unintended escape), which is then modified by attenuation or inactivation. These two types of whole virus vaccines are well-established in terms of technology and pathways to regulatory approval, and are generally relatively easy to manufacture. The Sinovac and Sinopharm vaccines are examples of an inactivated whole virus vaccine developed for COVID-19.

The subunit vaccine uses a different method of introducing viral material into the body. Purified pieces of viral material selected for their ability to elicit a strong immune response are used. The subunit can be part of a protein, a polysaccharide, or a conjugate between a protein and polysaccharide. In the case of COVID-19 vaccines, the 'spike' protein of the virus has generally been chosen to develop a protein fragment. As these fragments cannot cause disease, the risk of side effects is minimised. These types of vaccines are cheap and relatively easy to produce, and again have a well-established route to regulatory approval. The viral material is grown in living organisms, by genetically engineering bacteria or yeast (not the virus) to produce quantities of the fragment in question. The fragments are purified, and often need to be complemented by an adjuvant to boost the level of immune response. The Novavax COVID-19 vaccine is an example of a protein subunit vaccine.

Nucleic acid vaccines are a relatively new technology, and involve using DNA or RNA encoding of the antigen of interest. Prior to COVID-19 no nucleic acid vaccines had been approved for human use, although several DNA vaccines had been approved for animal use. Both types involve introducing genetic material into the host body's cells, so that those cells transcribe and/or translate the genetic material into protein, which is then presented on the host cells to stimulate the immune response.

With DNA vaccines, a piece of DNA is inserted into a bacterial plasmid, which is then injected into the individual, along with one of a number of technologies to assist the plasmid to penetrate into the host's cells.

RNA vaccines encode the protein of interest in messenger (mRNA) or self-amplifying RNA (saRNA). Unlike bacterial plasmids containing foreign DNA, the RNA in RNA vaccines is transitory as the RNA cannot replicate or integrate into host genetic material, and is therefore seen as safer than DNA vaccines. The RNA encoding the viral protein is injected alone, encapsulated with nanoparticles or driven into cells using similar techniques as for DNA vaccines. Due to the nature of DNA and RNA vaccines, it can be very quick to develop these once the viral DNA or RNA is known. In the case of COVID-19, its RNA was sequenced at a very early stage, allowing rapid development of mRNA vaccines.

Both types are relatively easy to manufacture, although as most readers will be aware, extreme (i.e. ultra-cold) storage conditions for nucleic acid vaccines are often needed to protect the genetic material to be injected. Examples of mRNA vaccines developed for COVID-19 are the Pfizer-BioNTech and Moderna vaccines that have received significant recent press coverage.

A final class of vaccine being developed for COVID-19 are the viral vector vaccines. These are similar to nucleic acid vaccines in that they do not directly introduce the whole or parts of the virus in question to stimulate an immune response, but instead use the body's own cells to manufacture the protein in question. In this case, genetic material encoding the protein in question is inserted into a different, non-pathogenic virus. This virus acts as a vector to deliver just the genetic material for the protein of interest. In each case the viral vectors are stripped of any disease-causing genes and sometimes also the genes allowing the virus to replicate.

Depending on the latter step, there are two types of viral vectors used. The non-replicating ones are unable to make new particles when they infect their target cells. Their role is simply to introduce the genetic material for the viral protein in question. Replicating viruses are also able to use the target cell's machinery to

produce additional viral vectors containing the genetic material of interest which can then go on to infect further cells, amplifying the level of production of the viral protein in question.

These types of vaccine are harder to produce on a large scale than the others, due to the need to produce large amounts of virus. Again, they are relatively new as a class, although previous human vaccines in this class had been approved (for example the Ervebo Ebola vaccine). The Oxford-AstraZeneca COVID-19 vaccine is an example of this type of vaccine, using an adenovirus (the common cold virus) as the vector.

But how do these vaccines take the leap from laboratory to hospital floor?

The regulatory questions

Under EU law, most COVID-19 vaccines in the EU must be approved under the centralised procedure, which is mandatory for any vaccine using biotechnology. These centralised marketing authorisations can only be granted by the European Commission upon favourable opinion of the EMA's Committee for Medicinal Products for Human Use (CHMP).

Vaccine development for COVID-19 vaccines is being fast-tracked globally, and the EU is no exception. The EMA created the COVID-19 Task Force (ETF) to support the Member States and the European Commission (EC) in taking rapid and coordinated regulatory action on the development, authorisation and safety monitoring of treatments and vaccines for COVID-19. Amongst other things the ETF reviews scientific data on potential COVID-19 medicinal products, engages with developers in preliminary discussions, offers scientific support to facilitate clinical trials conducted in the EU, provides feedback on development plans of COVID-19 medicines and advises the CHMP and the Pharmacovigilance Risk Assessment Committee. Importantly, it also ensures close cooperation with stakeholders and relevant European and international organisations.

To accomplish the above, rapid procedures have been established and are available for products intended for the prevention or treatment of COVID-19. In this framework, rapid scientific advice is provided in support of the generation of evidence for treatments and vaccines for COVID-19. It is an ad hoc procedure which follows the general principles of the regular scientific advice, but with adaptations to facilitate acceleration. This includes no pre-specified submission deadlines for developers to submit their submission dossier, flexibility regarding the type and extent of the briefing dossier (to be discussed on a case-by-case basis) and a reduction of the total review timelines from 40/70 to 20 days.

A rapid agreement of a paediatric investigation plan (PIP) and rapid compliance check is also in place for COVID-19 medicines. This means that applications for agreement of PIP, deferrals or waivers for treatments and vaccines for COVID-19 are reviewed in expedited manner, with a total evaluation time for a PIP (including waiver or deferral) of minimum 20 days, compared to the normal timeline of up to 120 days of active review. The compliance checks will also be expedited.

Rolling Review is an ad hoc procedure used in an emergency context to allow EMA to continuously assess the data, as they become available, for an upcoming highly promising application. There can be several Rolling Review cycles, with each cycle normally requiring a two-week review, depending on amount of data, with responses to list of questions from previous Rolling Review cycles to be incorporated into subsequent Rolling Review submissions.

The CHMP has recommended the granting of conditional marketing authorisations for the vaccines that have been approved by the EC so far. This is not a new type of marketing authorisation, but one that has been in place for a number of years and is envisaged for medicines addressing an unmet medical need (which is the case with COVID-19, as there exists no satisfactory method of diagnosis, prevention or treatment authorised in the EU),

and in emergency situations in response to public health threats recognised by the World Health Organisation or the EU.

The granting of this type of marketing authorisation with less comprehensive clinical data is justified provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

A conditional marketing authorisation is different from an emergency use authorisation, which some countries like the UK and the US are using to permit the temporary use of an unauthorised medicine in an emergency situation while it lasts. Whereas an emergency use authorisation is not a marketing authorisation, a conditional marketing authorisation is a marketing authorisation with less comprehensive clinical data, which can be used provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The marketing authorisations granted are subject to some post-authorisation conditions, like the need to monitor the clinical trial participants for an additional period of two years, to ensure that a full dataset will be available at some point for these medicinal products.

Happily, with the rollout of vaccines well underway, the COVID-19 pandemic at last appears to have an end date. And though we hope it should never come to it, the regulatory process to enable rapid rollout may yet provide a useful precedent when it comes to tackling the next global public health challenge.

Q&A: What does 2021 hold? The industry view

2021 looks set to be an exciting year for the biotech and healthcare sectors, commented **Yuung Yuung Yap**, Senior Global Legal Regulatory Counsel at global healthcare company **Viatris.**

"2020 was a momentous year for the sector, and biotech has arguably never figured more prominently in public consciousness. Crucially, the biotech sector enters 2021 from a position of strength, with heightened interest in the market, significant investment activity and real opportunities for all parties. It's an exciting time to be working in such an important, innovative industry.

"A defining feature of 2020 was collaboration, which played a huge role in getting vaccines developed and approved so quickly. It was a fine example of what we all know our sector can do. As companies, regulators and governments continue to work closely together, we may see 2021 remembered as the year the biotech and healthcare industries led the world safely out of the storm.

"When it comes to new frontiers, a market we're really keeping an eye on is China. It's an area of real growth and innovation, and I expect we'll be hearing a lot more of in the months and years ahead."

Viatris empowers people worldwide to live healthier at every stage of life, providing access to medicines, advance sustainable operations, and leveraging collective expertise to improve patient health across 165 markets globally.

Ground-breaking inventions: A tale of transgenic mice

Amidst the headline-grabbing disruption of COVID-19, one Supreme Court ruling - *Regeneron Pharmaceuticals v Kymab* - had an important impact on patenting in the biotech field.

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Partner

Kathryn Hambly
Associate

Although this might be understandable in the current climate, the implications of the ruling, which saw Regeneron's transgenic mice patents ruled as invalid for insufficiency, are of crucial significance for the biotech sector.

Indeed, the ruling cut to the core of a number of the key issues at play for many biotech companies, not only reinforcing the established case law of sufficiency, but also confirming that the standard for sufficiency cannot be lowered where a ground-breaking invention provides a 'principle of general application'.

The background: Mouse-human hybrids

The patents in suit relate to transgenic mice, namely those whose genomes have been genetically engineered to contain DNA fragments encoding functional gene products from other species (in this case humans). The mice are ultimately intended to be used to produce antibodies suitable for eventual use in human therapies.

By 2001, the priority date of the patents in issue, it had been observed that transgenic mice with fully human antibody sequences often displayed a poor immune response; they were 'immunologically sick'. Regeneron discovered that this was because the human constant region of the antibody interacted poorly with the downstream mouse immune response effector proteins. To overcome this problem Regeneron created antibody sequences in which the mouse constant region was maintained, but the mouse variable region genes were replaced with human counterparts. At the time this was a ground-breaking invention (a fact acknowledged by the Supreme Court). The hybrid gene structure was termed the 'reverse chimeric locus' and was the subject of several process and product patents filed by Regeneron.

The general understanding at the priority date was that hybrid genes containing more human variable region genes produced more diverse antibodies and were, therefore, more useful. However, at the time, it was not possible to combine the mouse constant region with the whole human variable region; indeed - far from it.

In 2013 Regeneron brought proceedings alleging infringement of its patents by Kymab's transgenic mouse, known as Kymouse. *Kymab* counterclaimed for revocation on the basis of insufficiency (as well as other invalidity attacks).

At first instance Henry Carr J construed the claims as extending to a range of transgenic mice, spanning those with only a few human variable region genes to those with a full human variable region. Carr J held that Kymouse infringed the claims but the claims were invalid for insufficiency because the skilled person would not have been able to make any of the claimed mice at the priority date.

The Court of Appeal agreed with Carr J's construction of the claims, but overturned his decision, finding the patents valid and infringed. The Court of Appeal held that while only some of the mice within the range could be made (i.e. those with a very small number of human variable region genes), the 'invention' for which protection was claimed was a 'principle of general application' because mice across the entire range claimed would (when eventually made) benefit from the invention by being cured of their immunological sickness. The Court found that this teaching was properly taught by the patent and therefore the sufficiency requirement was met.

To the Supreme Court

The question to be addressed by the Supreme Court was whether a product patent, the teaching of which enables the skilled person only to make some, but not all, of the types of product within the scope of the claim, passes the sufficiency test where the invention would contribute to the utility of all the products in the range, if and when they could be made.

In addressing this question the Supreme Court closely considered the 'patent bargain'. In return for a time-limited monopoly to work his or her patent, the patentee must disclose the invention to the public in enough detail to enable the skilled person to work that invention. Lord Briggs confirmed that, in the context of a patent claiming a range of products, the patentee is required to disclose enough information that, coupled with the CGK, would be sufficient to enable the skilled person to make substantially all of the embodiments of products within the scope of the claim's relevant range. It was also confirmed that a patentee may rely on a principle of general application if it would appear reasonably likely to enable the whole range of products within the scope of the claim to be made.

In light of these principles, the Supreme Court ruled that the Court of Appeal had erred in two respects. First, the Court of Appeal wrongly held that the contribution to the art in this case was the 'invention' (namely the 'reverse chimeric locus'), rather than the ability of the skilled person to make the product claimed. Second, the Court of Appeal had been wrong to say that a patent is sufficient if products within the claim cannot be made, as long as the benefit of the invention would be enjoyed over the whole range of the claim if and when those embodiments could be made in the future.

Lord Briggs characterised the Court of Appeal's reliance on a 'principle of general application' as giving a monopoly for unlocking benefits that would be realised in the future. Lord Briggs made it clear that any such principle must still actually make the embodiments within the claim available to the skilled person at the relevant date. The reverse chimeric locus does not in itself enable the products to be made. Rather, the reverse chimeric locus is the result of successfully making the products, the full range of which could not be done.

Their Lordships ruled 4-1 in Kymab's favour (Lady Black dissenting), finding Regeneron's patents to be invalid for insufficiency.

What does the future hold?

The Supreme Court's decision highlights a strict approach to sufficiency and the importance of fulfilling the 'patent bargain'. The Supreme Court described the sufficiency requirement as "*part of the bedrock of the law*", and noted that to water this requirement down would "*tilt the careful balance [...] in favour of patentees and against the public in a way which is not warranted by the EPC*".

A key aspect of the disagreement between the Court of Appeal and the Supreme Court seems to come down to a desire to reward a genuinely ground-breaking technology. How could Regeneron have properly claimed its invention in a way that would reward its contribution to such a fast-moving field as genetic engineering, but not be deemed insufficient? Perhaps by framing the claim as "*a method of curing immunological sickness in transgenic mice...*", as advocated by Lady Black in her dissenting judgment.

However, framing the claim in this way could have resulted in other insufficiencies such as excessive claim breadth. Lord Briggs acknowledged that the patentee might have had to confine itself to "*scant and short lived reward for their efforts and ingenuity*", but that what matters is the settled, strict reading of law that a product claim must properly enable the products to be made.

It is possible that the decision could fuel further insufficiency attacks on claims to broad ranges, not least in the form of 'Markush' formulae. Such a development would strike at the heart of the sector whose hallmark is arguably the continued development of ground-breaking technology. Only time will tell whether this is the case, but in the meantime, the Supreme Court ruling provides vital guidance.

*In **January** 2021, Cambridge biotech firm Kymab was acquired by Sanofi for a record-setting $1.1bn, the largest ever deal for a private British biotech company. Kymab is a clinical-stage company developing antibody treatments and immunology therapeutics and was the first company to be was spun out of the Wellcome Trust's Sanger Institute in 2010.*

International regulation for genome editing in 2021 and beyond

Ever since Crick and Watson discovered the double helix in 1953, many researchers, not to mention the public at large, have been captivated by the idea of altering genomes to avoid genetic disease. Ultimately, however, Heritable Human Genome Editing (HHGE)[1] is not just a question of scientific capability, but rather one of society and ethics, too.

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The issue was brought into sharp relief in 2018 when researcher He Jiankui announced that, by editing the DNA of healthy embryos, he had helped bring about the birth in China of two 'CRISPR babies'[2]. The scientific establishment erupted, but conceded the absence of international consensus. In response, the International Commission, convened by the US National Academies of Medicine and Sciences and the UK Royal Society, was established 'to determine whether the safety and efficacy of genome editing methodologies and associated assisted reproductive technologies are or could be sufficiently well developed to permit responsible clinical use of HHGE', and to define 'a responsible pathway for the clinical use of HHGE, should a decision be made by any nation to permit its use.'

The subsequent report, published in September 2020, could have significant implications for the continued development of genome editing in the months and years ahead.

Gene editing explained

'Gene editing' (GE) is the use of molecular tools to make precise alterations to DNA in order to correct, replace or add genes. GE is not new, but the appearance, nearly a decade ago, of CRISPR/Cas9 as a precision editing tool revolutionised biology[3], not least because of its simplicity, speed and cost. Obvious applications include correcting genetic pathologies at source to avoid or cure disease, or to improve the body's ability to fight it (as He had attempted, in disabling the CCR5 gene in efforts to immunise the infants from HIV), but distinguishing disease avoidance from *à la carte* trait selection may not be easy. For example, HIV avoidance may be a more legitimate goal in China than in, say, France. GE may lead to off-target edits and, in

1 National Academy of Medicine, National Academy of Sciences, and the Royal Society. Heritable Human Genome Editing. Washington, DC: The National Academies Press. 2020. DOI: 10.17226/25665. https://royalsociety.org/news/2020/09/heritable-genome-editing-report/

2 Not mentioning that the clinicians who implanted the GE embryos into a healthy mother were not informed.

3 The discovery secured Emmanuelle Charpentier and Jennifer Doudna a Nobel Prize in 2020. https://www.nobelprize.org/prizes/chemistry/2020/press-release/

embryos, 'mosaics' of edited and non-edited cells. CRISPR/Cas9 has given rise to ever more accurate versions, but quality control remains a paramount concern.

There are two forms of human GE: somatic and germline. Somatic GE involves alteration of genetic information in targeted cells in a person's body, that will not be inherited. Examples of somatic cell editing include therapies for cystic fibrosis and sickle cell disease, which involve localised edits to restore target tissues or cell types to 'normal' function. The European Medicine Agency addressed editing quality standards in a 2018 draft guideline[4], and therapies are showing considerable promise[5].

The other form of gene editing is germline editing. Here, edits are not only made prior to any person existing, but before embryological development. As cells multiply, genetic modifications are copied into all cells of the growing embryo and, should it be implanted (ie not used solely for research), into those of any eventual person. As this includes such a person's reproductive cells, edits may be passed down to children and enter the wider human genome. When editing may have transgenerational impacts, it falls under the term Heritable Human Genome Editing (HHGE). As the entire organism is affected, this form of GE is true 'genome editing'. How should humanity govern it?

The International Commission concluded its HHGE investigation with a list of 11 Recommendations setting out what it considers necessary for a responsible translational pathway to HHGE.

*Personalised medicine looks set for significant investment. With several hundred gene therapies under development by more than 30 drugmakers, the FDA expects 40 new treatments to have reached the US market by 2022. Opportunities for investment are ripe: since 2018, eleven drugmakers haveset aside **$2bn to invest** in gene therapy manufacturing.*

A pathway to clinical use

Recommendation 1 endorses the prevailing view in the scientific community that the possibility of making precise edits in human embryos efficiently, reliably and without undesired effects has yet to be established. The Commissioners did not recommend restricting research (using CRISPR in human embryo research is permissible in the UK subject to standard rules under the HFE Act 1990. It is not HHGE as edited genomes are not inherited.), but did consider that CRISPR germline editing should not be used clinically (ie HHGE) until certain criteria are met, offering detailed guidance on how the Commission thought HHGE trials should proceed. Some regret that the Commission did not recommend a moratorium, but others think it a sensible approach: if society accepts certain uses, HHGE may be made lawful subject to quality standards, even if *currently* unattainable.

4 https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically_en.pdf

5 https://www.globenewswire.com/news-release/2020/12/05/2140152/0/en/CRISPR-Therapeutics-and-Vertex-Present-New-Data-for-Investigational-CRISPR-Cas9-Gene-Editing-Therapy-CTX001-at-American-Society-of-Hematology-Annual-Meeting-and-Exposition-Together.html

A moratorium would probably have more totemic than practical value: if HHGE technology exists, parents wishing to have genetically-related children who are free of hereditable disease could probably circumvent any prohibition without being discovered.

The Commission identified six broad categories of potential clinical applications of HHGE, only two of which it said should be considered at this time:

i. cases of serious monogenic diseases (defined by the Commission as diseases caused by a mutation in a single gene, which causes severe morbidity or premature death) in which all of a couple's children would inherit the disease genotype or;

ii. serious monogenic diseases in which some, but not all, of a couple's children would inherit the disease genotype.

Recommendation 4 then set out criteria that the Commission believed should be met by any initial use of HHGE:

i. it should be limited to serious monogenic diseases;

ii. it should be limited to changing a pathogenic genetic variant known to be responsible for the serious monogenic disease to a sequence that is common in the relevant population and is known not to be disease-causing (sometimes referred to as a 'wild type' edit);

iii. only embryos in which the disease-causing genes have been edited should be implanted, to ensure that no resulting individuals are exposed without significant benefit to potential HHGE risks; and

iv. the use of HHGE should be limited to situations in which prospective parents:

a. have no option for having a genetically-related child that is free of serious monogenic disease, because without GE all their embryos would carry the disease variant or;

b. have attempted at least one cycle of preimplantation genetic testing without success, and only 25% or less of embryos would, without GE, be unaffected.

Some view these recommendations as endorsing a move to clinical HHGE, subject only to quality and ethical acceptance, that many clinicians consider unnecessary, arguing that preimplantation genetic diagnosis is more effective and less ethically problematic than HHGE, so that the number of parents who might benefit from HHGE may be vanishingly small. The Commission had anticipated this in point 4(ii) above. As PGD options are merely for or against implantation, a short supply of eggs may not qualify it as an ethical alternative to HHGE.

While some express concerns that already unequal access to reproductive healthcare may become more extreme in the case of GE, others speculate wryly that normal development may be threatened more by quality assessment requirements, such as the biopsy and monitoring of early GE embryos, than by the original editing process. Indeed, the Commission recognised that the need for such tests would be obviated if gamete progenitors were edited and tested for quality prior to fertilisation.

Notably, the Report encourages research on developing methods to produce functional human gametes from edited progenitors, highlighting an approach that, though far from ready, might provide prospective parents with a safer option for avoiding the inheritance of disease-causing genotypes than embryo editing: avoiding the hazards of embryo biopsy by preimplantation screening of gametes derived from a culture of edited progenitors.

Beyond the science

Although the Commissioners emphasised that HHGE invokes issues of ethics and society as well as of biomedicine and technology, some complained that their reluctance to pronounce upon ethics was an abnegation of responsibility. It's doubtful, however, that the Commission, which endorsed the view of the UK's Nuffield Council on Bioethics that engagement with publics should form an integral part of policy development, had a mandate to impose global ethical standards.

Recommendations 9-11 propose an international scientific advisory panel to monitor development of editing technologies and to assess their safety and efficacy. Though a whistle-blower mechanism may help to uncover unethical practice, the deterrent effectiveness of the recommendations seems questionable. Proposing that HHGE should not occur in places without appropriate expertise or regulation appears futile.

These are exactly the places where HHGE appears most likely, while its deterrent effect in places where HHGE is already prohibited, such as the UK and (debatably[6]) He Jiankui's China, seems improbable.

Equally vague is how the proposed panel would operate between existing international entities, such as WHO or UNESCO, and national laws, although a separate WHO inquiry has produced a draft governance framework[7].

6 https://www.bristows.com/viewpoint/articles/beware-of-cheap-imitations-justice-and-he-jiankui/

7 https://www.who.int/docs/default-source/ethics/governance-framework-for-human-genome-editing-2ndonlineconsult.pdf?ua=1

Data Transfers: Bump or mountain in the Road?

Collecting and transferring personal data is vital to biotech. After all, developing technologies to improve lives often depends on the collaboration of different companies and providers, and with it, the effective and often-seamless transfer of personal data, typically relating to patients, research participants, consumers, or others.

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As many biotech companies will be aware, the data protection landscape has changed considerably over the past decade, not least the specific ways in which personal data can be transferred across borders. In July 2020, for example, the European Court of Justice appeared to upend the transfer of data to the US almost overnight when it struck down the EU-US Privacy Shield, which had itself emerged from the wreckage of Safe Harbour.

Crucially, the striking down of the Privacy Shield in the Schrems II decision threw up a number of questions, and heightened obligations, for the significant number of biotech companies that are reliant on standard contractual clauses (SCCs) when exporting data outside if the EEA. But, as we enter 2021, what are the implications for biotech?

The current routes

Before delving into the decision and its implications, it may be helpful to look at the framework for transferring personal data more generally. Currently, if biotech companies are transferring personal data out of the EEA to a country considered by the European Commission to ensure an adequate level of personal data protection, they do not have to consider further compliance steps for the transfer. If there is no adequacy decision for the recipient country, appropriate safeguards are required. Failing this, companies may try to rely upon one of the limited exceptions under the legislation.

The two most common appropriate safeguard mechanisms are: SCCs, which are clauses approved by the European Commission and signed by the EEA data exporting and non-EEA data importing entities; or binding corporate rules (BCRs) for transfers between multinational group companies.

As the European General Data Protection Regulation (GDPR) applies in the UK, the transfer framework is the same for transfers of personal data out of the UK, and companies will be able to rely on the same mechanisms that they put in place to comply with the GDPR following Brexit. But when it comes to transfers from the EEA into the UK, appropriate safeguards are required unless the European Commission issues a UK adequacy decision, or a limited exception applies. At the time of writing, the clock is still ticking on an adequacy decision.

Our shields are down

Adequacy, it might be argued, will be the watchword of the data protection world for the next few years. Indeed, the Privacy Shield was, itself, a 2016 adequacy decision that held that its predecessor lacked sufficient protections. It too fell, however, when the CJEU considered the US government surveillance programmes to conflict with EU law, failing to grant individuals sufficient rights before the courts against US authorities.

The upshot was that many biotech companies quickly looked to put SCCs in place. But recent Guidance raises questions as to whether these are, indeed, the quick fix solution that many had hoped.

In particular, the part of the Decision that has raised the most questions is the fact that it requires data exporters and importers to verify, before a transfer, whether the EU level of data protection is respected in the recipient country. If not, the exporter (say a company conducting research in France) needs to implement "*supplementary measures*" to protect the data in the recipient country (say the United States, where the company commissioning the research is based). If equivalence with the EU data protection standard cannot be achieved, transfers must stop.

When it comes to what constitutes "*supplementary measures*", the European Data Protection Board Guidance[1] has provided examples of what these could look like; separating them into technical, contractual and organisational. Accompanying guidance on "*Four Essential European Guarantees*"[2] to factor into assessing the data protection environment of a recipient country has also been provided, and clarity guidance on how the Decision applies to BCRs is expected as well.

The Guidance raises significant challenges. The task of carrying out a risk assessment of a recipient country's data protection laws from an EU perspective is something that companies are grappling with. The main technical measures stated in the Guidance - encryption, pseudonymisation and splitting data up - may affect data usability. Some of the contractual measures, such as obliging a data importer to certify that the laws in the recipient country do not require it to operate back door access to personal data, may be ineffective where the importer is prevented from disclosing this information under applicable laws. Moreover, the objective approach to the assessment that is advocated by the Guidance appears to be contrary to the more risk-based approach that runs throughout the GDPR.

How to get to the other side?

Biotech companies will already have gone some way in mapping and considering their international data transfers, as part of GDPR compliance. They may also have taken data minimisation steps. Further actions could now include: documenting their approach to the steps in the Guidance; building sections into vendor due diligence questionnaires around data access in recipient countries; expanding data protection impact assessments to cover risks around personal data access and security in other countries; and encrypting/ pseudonymising particular data sets before

1 https://edpb.europa.eu/sites/edpb/files/consultation/edpb_recommendations_202001_supplementarymeasurestransferstools_en.pdf

2 https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_recommendations_202002_europeanessentialguaranteessurveillance_en.pdf

transfer, to the extent possible. Bolstered obligations can be added to contracts with service providers/collaborators in countries outside of the EU and UK around confidentiality and access to data, though some may be ineffective under applicable laws.

That said, the threshold for ensuring a compliant transfer of personal data using the SCCs has been greatly raised by the Decision and Guidance, and it is difficult to see how the requirements can be complied with fully without significant resources (including input from local lawyers).

Hopefully a different approach to privacy under the Biden administration can pave the way towards a Privacy Shield successor, and clear the congestion for transfers to the US. In the meantime, biotech companies should monitor for further developments in this area (including the new SCCs updated for GDPR purposes, expected early this year) and consider how they can build as much of the Guidance as they can into their current practices.

Parallel imports: The road ahead

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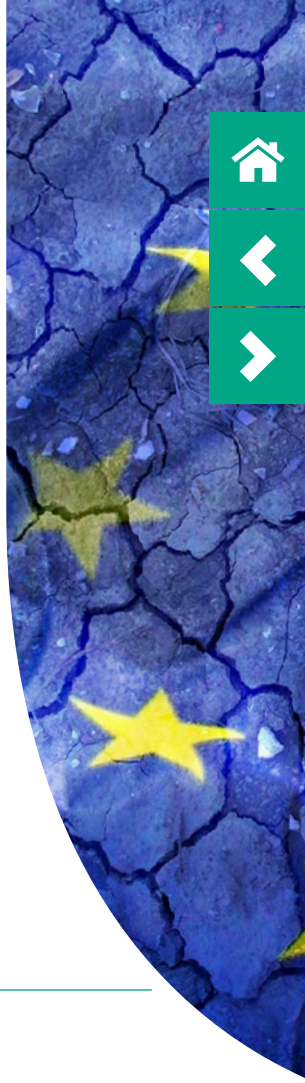


As we start 2021, Brexit has finally reached the tipping point, imposing a raft of new regulations and requirements on biotech businesses across the EU and the UK. Practically all firms in the biotech sector have spent much of the last few years preparing themselves for the UK's exit from the EU. However, as with many issues arising from Brexit, parallel imports are raising some questions, especially in such an IP-rich sector as biotech.

As we start 2021, Brexit has finally reached the tipping point, imposing a raft of new regulations and requirements on biotech businesses across the EU and the UK. Practically all firms in the biotech sector have spent much of the last few years preparing themselves for the UK's exit from the EU. However, as with many issues arising from Brexit, parallel imports are raising some questions, especially in such an IP-rich sector as biotech.

Where businesses who export IP-protected goods from the UK to the EEA are now required to have the right holder's consent, as putting goods on the market in the UK now no longer also counts as doing so in the EEA, the picture is different for those entering the UK from the EEA. Indeed, it might be said that for the latter it is business as usual.

Put simply, importing such goods into the UK will be permitted because the UK government has mandated that IP rights in goods placed on the EEA market by, or with the consent of, the rights holder, will continue to be considered 'exhausted' if they are then imported into the UK. Guidance issued by the UK government says that 'This means that parallel imports into the UK from the EEA will be unaffected.[1]'

But what does the law say?

The law relating to parallel imports has been developed continuously over the last 30 years, primarily through judgments of the CJEU. This body of case law will become 'retained EU law', and so lower courts will remain bound by it. More senior courts, including the Court of Appeal of England and Wales, will have the power to depart from it.

The fundamental purpose of allowing for EEA exhaustion is to ensure the smooth working of the internal EEA market. Over the years, in the context of parallel imports, expressions like 'avoiding artificial barriers to trade' and 'not partitioning the market' have been prevalent.

Once a good has been put on the market in the EEA by the brand owner, or with its consent, the brand owner has exhausted its exclusive right to first market the good. The brand owner can not oppose dealings in those exhausted goods unless those goods have not been previously been put on the market in the EEA by the owner, or with their consent, or there are legitimate reasons to oppose the further marketing. The whole premise is to

1 https://www.gov.uk/guidance/exhaustion-of-ip-rights-and-parallel-trade-after-the-transition-period

prevent a brand owner carving the EEA market into different areas, effectively continuing to control the after-market by relying on IP rights to prevent parallel imported products.

By way of example, in cases relating to the repackaging of goods (normally pharmaceutical), the courts assess whether it is necessary to do so, and an IP rights owner cannot rely on its rights to oppose repackaging where this would contribute 'to the artificial partitioning of the market'. Will the UK courts still apply this principle of preventing artificial partitioning of the market, where the UK is no longer part of that market and it is arguably 'artificial' to pretend otherwise? If 'parallel imports into the UK from the EEA will be unaffected', then the CJEU law that explains why intra-EEA parallel imports are legitimate must apply.

In other cases, the courts have considered whether the trade mark owner has 'consented' to their goods being placed on the market within the EEA, and certain facts have been found by the courts to amount to implied consent for such marketing. Once the UK leaves the EU, will this analysis stay the same? Or, will trade mark owners have stronger grounds to argue that they have not consented to any marketing which might lead to their goods being imported into the UK? Again, if 'parallel imports into the UK from the EEA will be unaffected' then surely that body of law must continue to be applied with regards to consent.

This is where things become odd.

Complicating matters

The underlying rationale of EEA exhaustion and the CJEU decisions only makes sense in the context of the functioning of the single market. For example, if considering whether goods have been put on the market in the EEA and thus can be exported to the UK, one has to consider a morass of case law about the meaning of 'putting on the market', all in the context of preventing barriers to trade in the single market. We will be applying law wholly designed to protect the integrity of the single market, despite of course no longer being in the single market. Of course, lots of EU (IP) law is framed with the functioning of the internal market in mind, however, parallel imports is an area where that premise has totally shaped the state of the law.

The above is particularly true in the field of medicinal products. Things become even more complicated when dealing with this type of product because of the highly harmonised EU bio-pharmaceuticals system. There is also the need to have a parallel import licence (for non-centrally authorised medicinal products) issued by the competent authority in the Member State of import, based on the similarity to a reference marketing authorisation of a product commercialised in the Member State of destination, or a parallel distribution notice (for centrally authorised medicinal products).

What will happen, going forward, when the marketing authorisation of reference upon which the parallel import licence has been issued ceases to be valid? In the *Ferring* case[2], the CJEU clarified that the automatic cancellation of a parallel import licence due to the withdrawal or expiry of the marketing authorisation of reference is contrary to EU law, as it is contrary to Article 34 of the TFEU. This approach was possible in view of the highly harmonised system for medicinal products in the EU, where pharmacovigilance in the Member State of importation can be guaranteed through cooperation with the national authorities of the Member State of exportation. Can the UK follow the EU's

2 Case C-172/00 *Ferring Arzneimittel GmbH v Eurim-Pharm Arzneimittel GmbH* ECLI:EU:C:2002:474

position now that there is no mechanism for pharmacovigilance cooperation with the national authorities of the EU Member States? More recently, in the *Kohlpharma* case[3], the CJEU considered whether a parallel import licence can be amended once the reference marketing authorisation has expired. It concluded that in situations where the marketing authorisation of the reference product in the Member State of importation has expired, a parallel importer should be able to update the documents and particulars relating to the medicinal product to be imported, on the basis of the documentation of another medicinal product with the same therapeutic indication which (i) is covered by an MA in both the Member State of importation and the Member State of exportation; and (ii) contains the same active ingredient but in a different pharmaceutical form.

Again, the decision was based on the fact that pharmacovigilance can ordinarily be guaranteed for medicinal products that are the subject of parallel imports, through cooperation with the national authorities of the other Member States, by means of access to the documents and data produced by the manufacturer in the Member States in which those medicinal products are still marketed on the basis of a marketing authorisation still in force. Will this retained EU law fit in the new framework, where the UK regulatory system will work independent from the EU? The only cooperation, relating to manufacturing, envisaged in the EU-UK Trade and Cooperation Agreement does not take us very far.

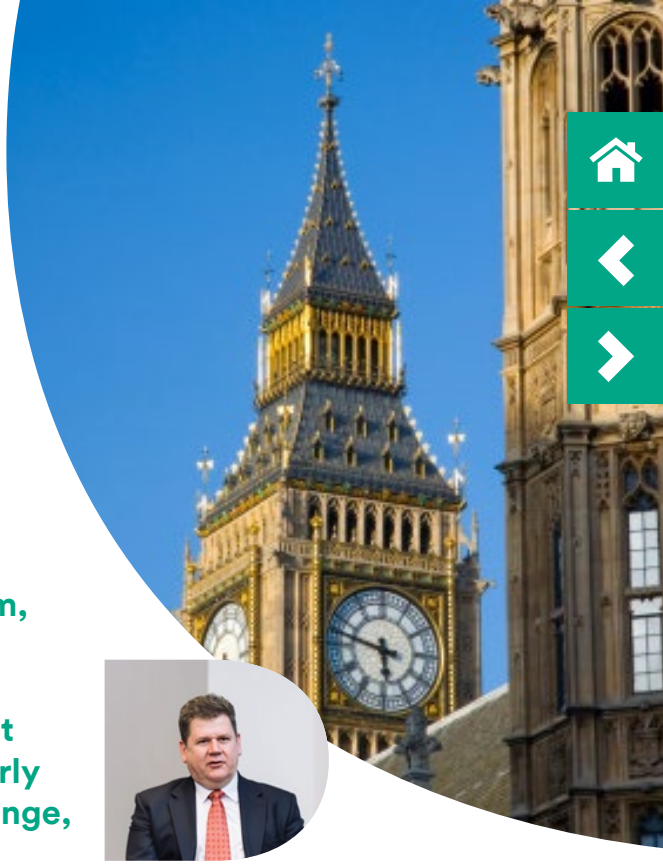
The UK will have to fill in some gaps to be able to rely on the retained EU law if it wishes to continue with the import of medicinal products from the EU. So far, the MHRA has only issued guidance on the process to convert parallel distribution notices for centrally-authorised medicinal into parallel import licences, as centrally authorised medicines will no longer be valid in Great Britain and, in turn, the EMA's parallel distribution notices will no longer be valid in this territory. This is welcomed guidance, but it does not address any of the open questions that relate to the parallel import of medicines from the EU to the UK.

When it comes to IP-protected goods in general, if the courts move away from the retained law and the UK forges its own rules, then this creates uncertainty for when and how parallel trade is legitimate or not.

The government has indicated it will consult on the policy in early 2021. If the government retains the EEA exhaustion policy, which might well be the appropriate policy at an economic level, hopefully it will grapple with the paradox of continuing to apply case law specifically designed to support the functioning of the single market.

In the meantime, it seems we will have to rely on all of the governing principles from the CJEU with respect to parallel imported products, until we are told otherwise.

3 Case C-602/19 *Kohlpharma GmbH v Bundesrepublik Deutschland* ECLI:EU:C:2020:804



Brexit Britain: Dumping ground or proving ground?

In the immediate aftermath of the EU referendum, there was a widespread hope across the life sciences sector that the UK would ensure its regulatory regime remained in lockstep with that of continental Europe. But despite reassuring early indications from lawmakers that little would change, what emerged in the Medicines and Medical Devices Bill proved to be almost as surprising as it was controversial.

Alex Denoon
Partner

Introduced in March 2019, the Bill affords the Secretary of State for Health the power to amend, by fiat, any regulation he or she might wish if it would thereby make the UK a more 'attractive' market for life sciences. Though near unprecedented in the extent to which the Bill transfers sweeping powers to the executive (which Lord Blencathra, Chair of the Delegated Powers and Regulatory Reform Committee, labelled an 'inappropriate delegation of power'), the measures are not without their supporters. Indeed, in the words of former Health Minister Baroness Blackwood, the Bill "*will slash red tape [and] support uptake of treatments for people with rare diseases*".

Whichever side proves to be correct, the Bill is hugely significant for the UK's life sciences market and will set the tone for years to come. Aside from the constitutional wrangling, the Bill throws up one question of particular importance: will post-Brexit Britain emerge as a life sciences proving or dumping ground?

It was inevitable that action would be taken post-Brexit to safeguard Britain's position as a premier life sciences hub. After all, a sudden secession or radical divergence from continental markets – home to almost half a billion consumers – risks seeing Britain drop precipitously down the life sciences pecking order. The UK could be left in the same position as Australia which, with its population of 25 million, rarely, if ever, sees new products launched until after the larger markets receive them.

The proving ground?

Though we cannot take it for granted that the Secretary of State will significantly alter the UK's regulatory framework with these powers, the early indications suggest that in the coming years, laws could be amended to allow developers to bring medicines to market in the UK before concluding Phase 3 trials.

While consumers might express worry about skipping a phase of trials in this way, life sciences professionals will recognise that, broadly speaking, preliminary safety of a new medicine is established after Phase 2 trials. As

a result, in certain circumstances there may be an ethical imperative to allow medicines to go to market before Phase 3 trials are concluded to determine their efficacy. This would not only mean that the UK could become a launching ground, but it is possible that pharmaceutical companies might also base their manufacturing operations in the UK, as close as possible to the initial market. If this occurs, the benefits for personalised medicine, cell & gene therapies, and medical device & diagnostic software in particular could be significant.

What's more, whilst Parliament often provides valuable oversight, once the UK leaves the EU it will lose the ability to quickly alter legislation in emergency situations, as the EU can (and does). The Bill may go some way to restoring this streamlined system in emergencies and will mitigate the occasions where Parliament can act as a brake to new life sciences regulation. The minor amendments to the Human Fertilisation and Embryo Act, for example, took 18 months to clear both chambers.

International context

Those debating the implications of the Bill frequently turn their eyes to Japan, which pioneered a similar 'adaptive' framework to encourage its stem cell sector. The Japanese stem cell market is widely touted as evidence that giving the executive the power to act swiftly does little to increase attractiveness or speed development. In truth, such a comparison is misleading: stem cell therapy remains a nascent sector because of current technological limitations that no amount of regulatory tweaking will overcome.

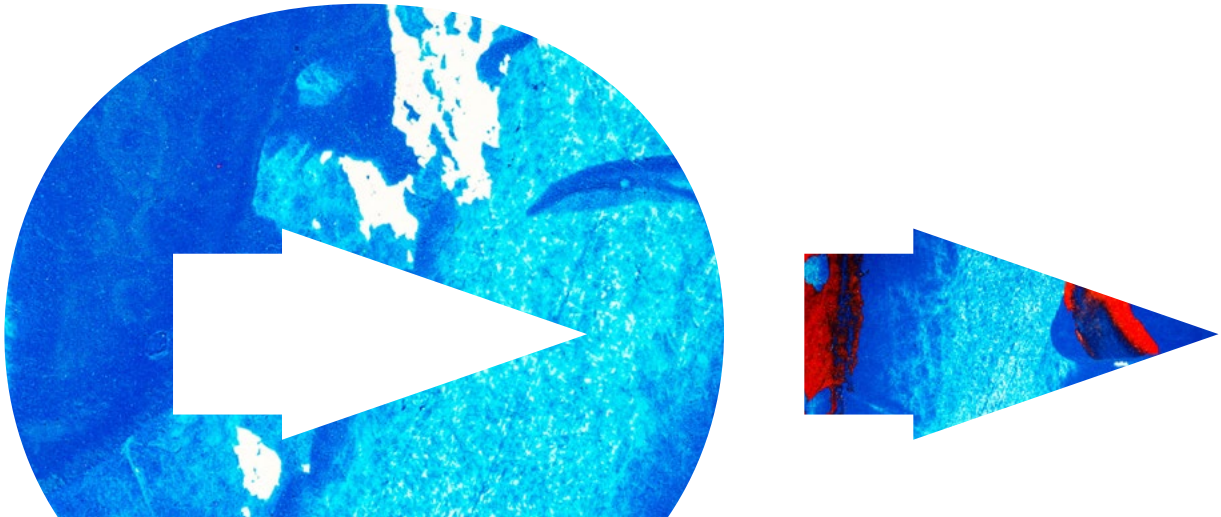
However, if the UK is breaking new ground, it may not be doing so alone. Not only does the European Commission possess significant powers to amend laws, but even Dr Jeffrey Shuren, a Director of the US' Food & Drug Administration, has sought to streamline regulatory approval, despite famously declaring that the US does not "*use our people as guinea pigs*". It would seem that the regulatory pendulum is pushing firmly in one direction: streamlining the regulatory approval process in the name of attractiveness.

The dumping ground?

Shuren's comments are also indicative of concerns that sudden changes to regulatory frameworks can turn states into dumping grounds for hastily-rolled-out products. There are legitimate concerns that headline-grabbing products will be approved on a whim by election-minded officials. Senior voices from within the sector, meanwhile, have expressed serious concerns that the Bill could drive significant market instability.

The Government has attempted to assuage such concerns by assuring the sector that it will go beyond its statutory obligation and ensure that no changes to the regulatory regime are made without an industry consultation. As we enter 2021, assuming the Government keeps its word, this presents opportunities for companies within the sector to have their voice truly heard, to help shape the new framework.

Whether Britain becomes a proving or dumping ground may yet be in the sector's hands.



The small difference making big waves: Why 'genetically engineered' is not the same as 'genetically modified'

The divide between genetically edited (GE) organisms and genetically modified (GM) organisms is seemingly just a single letter, but this small difference is causing significant discussion across the globe.

Julian Hitchock
Of Counsel

Of course, this is a rather reductive summary; for the full story we will need to jump back three years.

In 2018, the gene editing world was aghast when the EU Court of Justice decided in *Confédération paysanne*[1] to include GE organisms within the definition of GMO under the EU GMO (Deliberate Release) Directive (GMO Directive)[2]. The effect of the decision remains highly ironic: organisms whose genes are modified by exquisitely precise processes are heavily regulated, while those modified randomly are exempt[3]. The decision offended in other ways, ignoring the warning of the court's legal advisor to leave law-making to lawmakers[4].

That September, leading UK scientists called upon Cabinet Minister Michael Gove for a UK response[5], which he pronounced a Brexit opportunity. The following Summer, the new Prime Minister, Boris Johnson, used his maiden speech to Parliament to declare that Brexit would 'liberate the UK's extraordinary bioscience sector' from Europe's anti-GM rules, and the following May, the All Party Parliamentary Group on Science & Technology in Agriculture proposed that the UK definition of GMO under the Environmental Protection Act 1990 (derived from EU law) be restricted to 'the insertion of viable, heritable, foreign DNA', which 'would at a stroke remove around 90% of gene editing applications from the scope of GM regulation.'

1 http://curia.europa.eu/juris/liste.jsf?language=en&num=C-528/16

2 *Directive 2001/18*. (Implemented in the UK in the *Genetically Modified Organisms (Deliberate Release) Regulations 2002* (SI 2002/2443) https://www.legislation.gov.uk/uksi/2002/2443/contents/made

3 https://www.labiotech.eu/regulatory/gmo-regulations-europe/

4 http://curia.europa.eu/juris/document/document. Para 149.

5 http://www.cpm-magazine.co.uk/wp-content/uploads/2018/09/180903-Michael-Gove-letter.FINAL_.pdf

The Secretary of State responded, describing GE as 'a more targeted form of conventional plant breeding', but adding that the government 'would not propose changing at all the regulatory framework on GMOs.' Although a gene editing amendment[6] did appear in the Agriculture Bill[7], it was subsequently withdrawn[8] with the promise of a consultation[9] instead, a DEFRA spokesperson stating the government's opinion that 'organisms produced by … gene editing should not be subject to genetic modification regulation if the changes to their DNA could have occurred naturally or through traditional breeding methods.'

Crucially, though, the UK is far from alone in seeking to reform GMO regulation. In the EU, the clamour for change is coming from an unexpected quarter and, as we shall see, is being intensified by the COVID-19 pandemic.

GMO Regulatory Reform in the EU

Across the Channel, EU States had been waiting for a Commission policy on new breeding techniques long before *Confédération paysanne*. Rather than twiddle its thumbs, Sweden chose not to regulate some GE Arabidopsis plants on the basis that introducing DNA from another species and editing a plants' existing DNA are very different processes. Because most GE applications do not involve the former, any interpretation that subjected them to GM rules would severely restrict the choice of crops that EU farmers could grow. Although its position was blocked by the Court's decision, Sweden and others objected that the judges had failed to define which techniques were captured by the term used by the court, 'directed mutagenesis', which never explicitly referred to editing. The case had concerned herbicide-tolerant seed varieties, but how broadly should it be applied? It wasn't even clear how GE-restrictions could be enforced. [10]Despite claims by Greenpeace, there is no such thing as a GE crop test.[11]

Subsequently, in November 2018, the European Commission's Group of Senior Scientific Advisers publicly responded[12] that scientific knowledge and recent technical advances had rendered the GMO Directive unfit for its intended purpose, while a European Citizens' Initiative named Grow scientific progress, following in its wake, demanded a review of the regulation.[13]

Momentum built. In July 2020, EU-SAGE[14] published an open statement on behalf of its 132 European research institute members, recommending the EU to endorse GE for the welfare of its citizens, on the basis that it offers 'a more efficient selection of crops that are climate resilient, less dependent from fertilizers and pesticides' which would 'help preserve natural resources.' In the same month, the Conseil Européen des Jeunes Agriculteurs (CEJA[15]), representing around two million young European farmers, expressed frustration at the Commission's 'Farm to Fork' plan to make Europe's food system the global standard of sustainability, complaining that if they were to achieve F2F's goal of switching 25% of agricultural land to organic farming and reducing fertilizers use by 30 per cent, they would need access to GE products[16].

6 https://www.theyworkforyou.com/lords/?id=2020-07-28b.204.0

7 https://geneticliteracyproject.org/2020/07/30/gene-editing-amendment-to-uk-agriculture-bill-withdrawn-delaying-farmer-access-to-crispr-crops/ The [Act passed 11 November 2020.

8 https://www.euractiv.com/section/agriculture-food/news/uk-gene-editing-amendment-withdrawn-but-government-commits-to-consultation/

9 https://consult.defra.gov.uk/agri-food-chain-directorate/the-regulation-of-genetic-technologies/

10 Despite Greenpeace claims, there is no such thing as a GE crop test. https://twitter.com/methylcytosine/status/1303225481009991680?s=20

11 https://consult.defra.gov.uk/agri-food-chain-directorate/the-regulation-of-genetic-technologies/

12 https://op.europa.eu/en/publication-detail/-/publication/a9100d3c-4930-11e9-a8ed-01aa75ed71a1/language-en/format-PDF/source-94584603

13 The petition closed in July 2020. https://www.growscientificprogress.org/

14 European Sustainable Agriculture through Genome Editing network.

15 https://www.ceja.eu/home

16 https://www.euractiv.com/section/agriculture-food/news/young-farmers-need-a-toolbox-as-broad-as-possible-to-achieve-farm-to-fork-goals/

An unlikely champion?

By now, support had come from a surprising source: the most senior members of the Green Party of Europe's most GMO-conservative state, Germany, who had just endorsed the view of the Commission's Senior Advisors[17]. 'Current GMO regulation no longer corresponds to the current state of science', they stated: 'the decisive factor is not the technology but the result'. Strikingly, the Greens emphasised that 'it is not enough to describe a technology as 'more natural' or 'safer' if there is no concrete evidence to support it… In agriculture, biodiversity can be damaged just as much by organic products as by genetic engineering,' which, they wrote 'has fundamentally changed in the last ten years.' Sustainability required re-appraisal of new technologies, said the scientific Greens, warning that regulatory costs impeded competition and the emergence of more environmentally-friendly start-ups[18].

Meanwhile, the SARS-Co-V-2 pandemic had struck, and Germans discovered that a home-grown company was preparing to produce the first COVID-19 vaccine. Not just any vaccine, but the world's first mRNA vaccine. To expedite availability of mRNA vaccines, the European Parliament adopted[19] a 'temporary' regulation[20], a press release explaining that 'Some COVID-19 vaccines and treatments already being developed may be defined as GMOs[21]. As national requirements to assess the environmental risks of clinical trials on medicinal products that contain or consist of GMOs vary considerably across member states, a derogation from these rules is needed to avoid significant delay in developing life-saving vaccines[22].'

The following month, opening a GE debate in the Bundestag[23] by referring to the imminent release of BioNTech's mRNA vaccine, Dr Volker Wissing[24] highlighted the genetic technology linking medicine and food production. Rather than restricting GE research, said Dr Wissing, Germany should encourage it, 'if only to remain a competitive export nation.' A Green Party motion along traditional lines was dismissed, but within the Party, opinions were dividing. Its scientific wing now had backing from over 150 independent academics for a policy proposal that expressed openness to a 'fact-based assessment of new genetic engineering processes', and another group also showed a change of heart.

As approval of the first mRNA vaccines approached, the pressure to permit GE organisms grew across Europe. In October, a report on GE crop regulation by the European Federation of Academies of Science and Humanities had issued a direct appeal to EU leaders in Europe[25]. Warning of the dangers of failing to reform Europe's GM laws, the Federation declared that, 'in the circumstances, doing nothing does not seem to be an option.' The same month, when approving the 'Farm to Fork' scheme, EU Agriculture ministers, called for 'new and innovative techniques to boost sustainable food production, as long as they are shown to be safe for humans, animals and the environment', – a clear reference to GE agricultural products.

17 https://www.gruene.de/artikel/neue-zeiten-neue-antworten-gentechnikrecht-zeitgemaess-regulieren

18 *"New times, new answers: regulating GM law in a contemporary way"*.

19 July 2020. Parliament voted via the urgent procedure 505 votes to 67 in favour of the derogation, with 109 abstentions.

20 In accordance with the Commission's COVID-19 Vaccine Strategy.

21 https://www.europarl.europa.eu/news/en/press-room/20200706IPR82731/parliament-to-allow-COVID-19-vaccines-to-be-developed-more-quickly

22 https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en

23 https://www.bundestag.de/dokumente/textarchiv/2020/kw47-de-gentechnik-806836

24 Minister of Economics, Transport, Agriculture and Viticulture in Rhineland-Palatinate (FDP Party).

25 https://allea.org/wp-content/uploads/2020/10/ALLEA_Gen_Editing_Crop_2020.pdf

Where are we now?

As citizens impatiently await their mRNA vaccination[26] – a product with robust efficacy data[27], a safety record that grows jab by GM jab, and the prospect of saving the lives of millions – today may not be a good time to be anti-GM.

Is the EU likely to move GMO regulation to a more scientific basis? In an age of concerted disinformation in which populist parties expressly devalue scientific expertise and consciously sow distrust, this would be a remarkable turn of events. But in the pandemic's battle between frauds[28] and facts, there can only be one winner. As GMOs vindicate themselves in fighting the global challenge of infectious disease, rules that hobble their capacity to combat the challenges of food security, energy and climate look increasingly out of place.

As a first step, might expert regulators be given the power to classify products as GMOs if they incorporate transgenes, but not if their DNA has merely been edited and they pose no realistic risk to humans, animals and the environment? We may find out In April, when the European Commission reports to the Council on the impacts of new genomic techniques and the effect of *Confédération paysanne*[29].

26 EMA approval of BioNTech/Pfizer's mRNA vaccine by EMA: 21 December 2020.

27 Phase III data shows 95% effectiveness of Pfizer BioNTech (link) and 94.1% (with 100% efficacy against severe COVID-19) from Moderna.

28 https://www.acsh.org/news/2020/12/27/fraud-doctor-andrew-wakefield-now-lying-about-covid-rna-vaccine-15240

29 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019D1904&from=EN ; https://ec.europa.eu/food/plant/gmo/modern_biotech/new-genomic-techniques_en

CRISPR-Cas9 – from Nobel prizes to priority

Against the backdrop of a year characterised by heightened awareness of the biotech and pharmaceutical sectors, the Nobel Prize in Chemistry 2020 was fittingly awarded to Emmanuelle Charpentier and Jennifer Doudna for their contributions to the development of CRISPR-Cas9 gene-editing.

Nick Michelmore
Associate

The boundless potential of this technology demonstrates that the industry can not only defend society against a dire pandemic, but also shape the very future of health. Indeed, the press release issued by the Royal Swedish Academy of Sciences when awarding the Nobel Prize pithily summarised the technology in its headline: 'Genetic scissors: a tool for rewriting the code of life'[1], telling wording for the immense potential of Charpentier and Doudna's discovery.

As often seen with ground-breaking technology, disputes have arisen concerning its intellectual property and last year saw a patent case relating to CRISPR-Cas9 before the Technical Board of Appeal of the European Patent Office (EPO)[2]. The Board's decision in this case emphasises an important point for patent applicants: it remains vital to get the small formalities correct, no matter how significant the invention.

From lab to patent office

For quick context, as many readers will know, the CRISPR-Cas9 technique allows specific DNA sequences in virtually any genome to be located and edited or modified with relative ease. The specificity and accuracy of the technique has led to comparisons being drawn with the search function of modern word processers, and the potential applications range from medicine to agriculture to biofuels.

The case in question concerned an appeal against a decision in opposition proceedings brought by nine opponents to the patent. The Opposition Division had revoked the patent for lack of novelty over two pieces of prior art. This resulted from the finding that the patent was unable to make a valid claim to priority under Article 87(1) European Patent Convention (EPC) from certain US provisional applications. In its decision, the Opposition Division had applied the established case law in relation to the assessment of priority claims under Article 87(1). This is the so-called 'all applicants' requirement: all persons listed as applicants in a priority application must be listed as applicants for the subsequent application claiming priority (allowance being made for

1 https://www.nobelprize.org/prizes/chemistry/2020/press-release/

2 T 0844/18 (16 January 2020)

successors in title). The patent in this case had one applicant who was listed in the priority applications but who was missing from the later applications. The Opposition Division had thus held that the patent was not entitled to priority, leading to the finding of lack of novelty over two pieces of prior art published after the priority date.

Then the appeal

The appellants (the patent's proprietors, The Broad Institute, MIT and Harvard) challenged the legitimacy of the 'all applicants' approach. The appeal drew a lot of attention not only because of the subject matter of the underlying invention, but also because the appellants were challenging the EPO's rather formalistic approach to priority entitlement which had frustrated many patentees in the past, and is viewed by some as both unnecessary and readily utilised by third parties to invalidate otherwise good patents. In particular, the 'all applicants' approach is problematic for patents claiming priority to US priority applications (such as in this case) because of the requirement in the US to name the actual (and often numerous) inventors as applicants, even if their rights were assigned, for example, to their employer.

*Inevitably, COVID-19 is driving significant growth and will figure prominently in the sector in the year ahead. Pfizer, for example, expects to produce 50m vaccine doses in 2020, and a further **1.3bn by 2021**. The ventilator market grew by almost 200% in 2020, with the sector expected to be worth $7.72bn in 2020.*

The appellants set out their case in the form of three questions, and the Board dealt with each in turn:

1. Should entitlement to priority be assessed by the EPO?

The appellants argued that the EPO should not assess priority entitlement as a matter of principle because the 'all applicants' approach results in issues of title raised by non-owners being used to destroy the underlying property right. The priority right should only be challenged by someone claiming to be the rightful owner. However, the Board disagreed. The EPC clearly sets out requirements for priority and the EPO is empowered and obliged to assess the validity of a priority right claim. There are many formal requirements under the EPC and the loss of a patent due to failure to fulfil such formalities is a feature of the EPC system. In the present case, the appellants had not complied with the well-established practice of the EPO. It was not for the Board to repair such errors.

2. How is the expression 'any person' in Article 87(1) EPC to be interpreted?

In relation to this question, the appellants argued that 'any person' in Article 87(1) EPC must be interpreted to mean that anyone who duly filed the priority application (or his/her successor in title) can validly claim priority. Namely, if there are multiple applicants for the priority application, one, a plurality, or all, can validly claim priority. The 'all applicants' approach merely created additional obstacles for patentees. For the protection of third parties, the most important consideration for priority claims was not 'identical applicants', but that the same invention was being claimed.

For this question, the Board turned to the object and purpose of the 1883 Paris Convention for the Protection of Industrial Property (from which the requirements in Article 87(1) EPC derive), as well as to public policy considerations. The legal concept of priority in the Paris Convention allows applicants to be treated as if they

had simultaneously filed the same patent application in a multiplicity of member states (something that was physically impractical if not impossible in 1883). It is this legal fiction of simultaneous filing that establishes the 'all applicants' requirement. If a group of persons decides together to carry out an act of filing, then they must act in unison for this purpose. The bar for overturning long established case law and practice should be a high one and the appellants were faced with over 100 years of consistent case law on this point. In light of the above considerations, the Board rejected the appellants' argument and held that the 'all applicants' approach was the correct one.

3. Does national law (in this case US law) govern the determination of 'any person' who has 'duly filed' in Article 87(1) EPC?

With regards to this third question, the appellants had argued that the national law where the priority application was filed should be used to determine the meaning of 'any person'. This is because the right arises at the time (and therefore in the country in which) the priority application was filed. In this case, the national law would be US law (under which the applicant's status is tied to the degree of inventorship). Addressing this final point, the Board noted that the US is a signatory to the Paris Convention and therefore, in accordance with the US Constitution, the Paris Convention forms part of the 'supreme Law of the Land' in the US. Hence, it is the Paris Convention, rather than national law, that determines the meaning of 'any person'.

Referral to the Enlarged Board of Appeal

The minutes of the final day of the hearing suggest that the Board quite seriously considered a reference to the Enlarged Board of Appeal. Ultimately, the Board's view was that this was not necessary. The EPO had, without exception, adopted a consistent interpretation of Article 87(1) EPC since the inception of the European patent system and the Board thus felt able to answer the questions raised beyond doubt. The Board therefore disagreed with all three arguments put forward by the appellants and the appeal was dismissed.

There appears to be a growing global dispute between some of the key players of the CRISPR-Cas9 story, who are fighting for patent protection for this award-winning biotechnology. In this case the appellants' efforts to change the EPO's practices on priority were ultimately unsuccessful. The Board of Appeal made a clear statement that the 'all applicants' approach to priority entitlement is the correct one.

It is somewhat ironic that failure to comply with a century-old formality was capable of undermining a patent covering a biotechnology that may significantly impact the century to come. At least in the shorter term, 2021 and beyond will likely see more interesting disputes concerning patent protection arising from CRISPR-Cas9.

Neurim and Flynn v Mylan: The price spiral argument under scrutiny

It has long been argued before the English courts (and generally accepted albeit that evidence is required) that if an allegedly infringing generic product is allowed to launch prior to trial, this will lead to an irreversible price spiral for the patentee's product which cannot be compensated for in damages.

Aida Tohala
Associate

So, when the Patents Court[1], and then the Court of Appeal[2], did not accept the price spiral argument in *Neurim and Flynn v Mylan* in refusing to grant Neurim an interim injunction, notwithstanding Mylan's failure to clear the way, practitioners took note. But what do these two interim judgments contain, and what might they mean for pharmaceutical cases more generally?

The first refusal

The case concerned Neurim's patent to a prolonged release pharmaceutical formulation of melatonin, to improve restorative quality of sleep in patients suffering from primary insomnia. Neurim licensed Flynn, under which Flynn sells a product falling within the patent, Circadin®, in the UK.

Mylan sought to launch its generic product as soon as possible, but agreed not to launch until the application for interim relief was decided. Meanwhile, the main action trial was expedited and scheduled for October 2020.

On 3 June 2020, Marcus Smith J in the Patents Court refused Neurim's application for an interim injunction against Mylan. Applying the two-step *American Cyanamid* test, he first decided that there was a serious issue to be tried (as Mylan admitted). However, he then held that damages would be an adequate remedy for Neurim in the absence of an interim injunction. He made that decision by reference to two periods: (i) the period until the decision on the merits would be handed down; and (ii) the period from the end of the first period until patent expiry.

The appeal

The appeal was expedited and heard via remote video-conferencing on 18 June 2020. Neurim argued that damages would not be an adequate remedy in the absence of an interim injunction. It said it would suffer pecuniary loss (from lost sales and a downward price spiral that would be caused by Mylan's launch), plus consequential losses (like the inability to fund R&D or the education programmes needed to make Neurim's pipeline products profitable).

Mylan denied that a price spiral would follow or that there would be consequential losses, because it said the Claimants had enough cash reserves that could be used instead of the lost revenue. (In other words, they could afford it.)

Neurim also argued that the judge at first instance failed to take account of: (i) the consequential loss, (ii) the consequence of giving a green light to other competitors, and (iii) the significance of the consequences of generic entry 2 years and 3 months prior to patent expiry.

1 [2020] EWHC 1362 (Pat)

2 [2020] EWCA Civ 793

On 24 June 2020, the Court of Appeal dismissed the appeal. Floyd LJ, giving the judgment, disagreed with Neurim's submission that the first instance judge should have accepted the Claimants' evidence on consequential loss. Floyd LJ held that the judge was bound to examine the claims made in the evidence with a critical eye given the very short period of generic competition which the Claimants would have faced in light of an expedited trial date, which was just over four months. He also noted that the Claimants' evidence on consequential loss was served before the trial date was expedited and, therefore, was based on a much longer period than eventually anticipated.

As for the price spiral point, Floyd LJ held that that the evidence did not establish that the launch of a second generic product (in addition to that of Mylan) in the four months to trial was possible. He also noted that 53% of the Claimants' market was branded prescriptions which are protected from generic competition and that the Claimants could be expected to retain a portion of the remaining market. He decided that if Neurim and Flynn won at trial, it would be relatively straightforward to calculate the damages for the interim period in which Mylan would have been on the market. This would be assisted by: the Appellants' forecasts of expected sales revenues for the period up to the interim hearing and up to trial; both parties' actual sales figures and prices at which they sold; and the fact that the depressed price for the period between the interim hearing and trial would be known.

Implications for interim injunctions in future cases

Floyd LJ went out of his way to say that he disagreed with Neurim's submission that the decision would have grave consequences for the pharmaceutical industry generally. He denied that he had decided a generally applicable principle, highlighting the 'extremely unusual facts of this case'. He also noted that, while in many pharmaceutical patent cases courts have decided that lost sales and price depression losses amounted to unquantifiable loss, it was unhelpful to compare cases as the outcomes are heavily fact-specific.

So, is the decision such a marked change of course in the pharmaceutical landscape? Possibly not. It is fair to say that Floyd LJ made a point of emphasising the significance of the particular factual matrix to his decision. That being said, it will be interesting to see to what extent the decision is self-contained or whether future courts will place weight on whether patentees with significant cash buffers can 'afford' their losses.

Furthermore, the emphasis on the need to prove quick succession of competitor entry may have more impact in the context of biosimilar litigation, as it may be less likely for there to be multiple biosimilars ready to launch in quick succession, thus leading to the noted price spiral prior to trial (given the increased difficulty with obtaining regulatory approval for biosimilar products, and indeed in their manufacture).

What's next?

As a subscript to the interim injunction application, Neurim applied to the Supreme Court for permission to appeal the decision to refuse the relief. The Supreme Court declined to give permission to appeal, but in giving its (brief) reasons, the Court indicated that it may be time to revisit the *American Cyanamid* principles to be applied when determining whether to grant an interim injunction. However, in light of the short remaining period to trial, the Court refrained from taking up that challenge in this particular case.

Following the hearing of the expedited trial in October 2020, on 4 December 2020, the Patents Court provided its judgment in the main action. Marcus Smith J found Neurim's patent to be valid and infringed. However, the same patent was subsequently invalidated for insufficiency at the EPO following the TBA hearing on 17 and 18 December 2020. As such, as per the Supreme Court's decision in Virgin *Atlantic v Zodiac*[3], Neurim will not be able to claim damages in the UK for infringement of the UK designation notwithstanding its success on the merits in the UK.

3 *Virgin Atlantic Airways v Zodiac Seats UK (f.k.a. Counter Aerospace)* [2013] UKSC 46

Another year of SPC updates: Functional claims and new therapeutic applications

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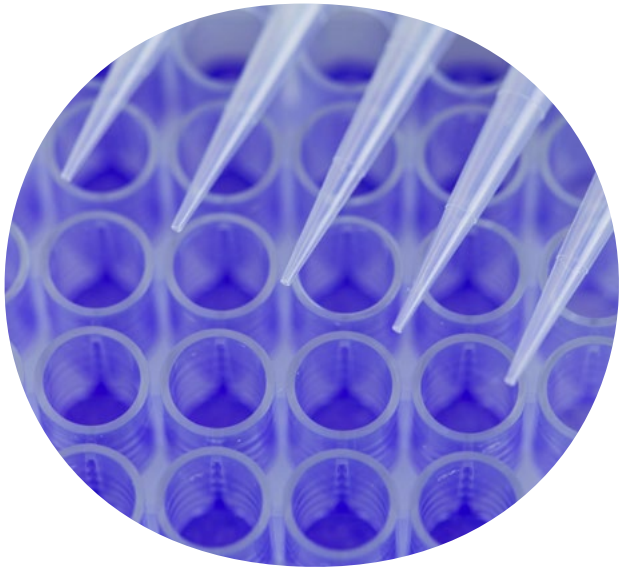
Article 3 of Regulation (EC) No 469/2009 (the 'SPC Regulation'), which establishes eligibility for a Supplementary Protection Certificate (an 'SPC'), has given rise to numerous preliminary references to the Court of Justice of the European Union (the 'CJEU'). Indeed, over the course of the last few years, the legal landscape for SPCs has been punctuated by a number of important decisions from the CJEU.

In this respect, 2020 was no different as the CJEU handed down judgments in two preliminary references – Case C-650/17 (*Royalty Pharma*)[1] and Case C-673/18 (*Santen*)[2].

Royalty Pharma & functional claims

Functional claims are of particular importance in some biotech inventions, not least, for example in relation to antibody products that are frequently claimed by reference to their binding characteristics. Despite the fact that the CJEU stated in Case C-493/12 (*Eli Lilly*)[3] that an active ingredient could be protected by a functional claim where 'the claims relate, implicitly but necessarily and specifically, to the active ingredient in question', the ability of such claims to form the basis of an SPC application, under Article 3(a) of the SPC Regulation, has remained an area of some debate.

In 2017, the Federal Patent Court of Germany (Bundespatentgericht) made a reference to the CJEU in *Royalty Pharma* regarding the interpretation of Article 3(a) of the SPC Regulation in the context of functional claims.



1 Case C-650/17 *Royalty Pharma Collection Trust v Deutsches Patent- und Markenamt* ECLI:EU:C:2020:327

2 Case C-673/18 *Santen SAS v Directeur général de l'Institut national de la properiété industrielle* ECLI:EU:C:2020:531

3 Case C-493/12 *Eli Lilly and Company Ltd v Human Genome Sciences Inc.* ECLI:EU:C:2013:835

Royalty Pharma held a patent for the use of DPP-IV inhibitors in the treatment of diabetes. They sought an SPC in Germany based upon this patent and the MA for a DPP-IV inhibitor, sitagliptin. Sitagliptin fell within the scope of *Royalty Pharma's* patent, but was not individually claimed or disclosed. Furthermore, and a separate point of interest for this case, sitagliptin was independently developed and sold by Merck Sharp & Dohme, which itself holds a later patent for the sitagliptin compound.

The German court referred three questions to the CJEU, asking whether a product is protected by a basic patent in force when it is:

i. part of the subject matter of protection defined by the claims and is provided as a specific embodiment;

ii. within a functional claim, but not provided as a specific embodiment elsewhere in the patent; or

iii. within a functional claim, but was developed after the filing date of the patent as a result of an independent inventive step.

In its decision, the CJEU confirmed that the relevant test for Article 3(a) had been set by the CJEU in Case C-121/17 (*Teva*)[4] and that this test applied to all products, not just the combination products which were the subject of the preliminary reference in *Teva*.

To recap, the test in *Teva* states that for a combination product to be 'protected' by the basic patent under Article 3(a), the claims need not expressly mention the combination but must relate to it necessarily and specifically. This will be the case, if from the point of view of the skilled person and on the basis of the prior art at the filing date or priority date of the basic patent:

i. the combination itself necessarily falls under the invention; and

ii. each of the elements in the combination must be specifically identifiable in light of all the information disclosed in the patent.

In its decision in *Royalty Pharma*, the CJEU has clarified that a functional claim is not precluded from protecting a product under Article 3(a) of the SPC Regulation, provided that the claims can be understood, in light of the description of the invention, to relate 'implicitly but necessarily' to the product in question. The CJEU confirmed that this assessment is undertaken by the skilled person at the priority date in light of their 'general knowledge' as well as the 'state of the art'. The CJEU further clarified that the product does not need to be included as a specific embodiment provided it can be specifically identified by the skilled person at the priority date of the patent.

The decision is therefore important in reconfirming that SPCs are available for products covered by functional claims. However, it remains to be seen how the test set out by the CJEU in *Royalty Pharma* may be applied in the context of antibody products. Perhaps unsurprisingly, given that sitagliptin is a small molecule, the CJEU gave no guidance as to how an antibody claimed by reference to its binding characteristics could satisfy the test in *Teva* (as interpreted by the CJEU in *Royalty Pharma*) in circumstances where it is not individually named or depicted in the patent.

The decision also raises some further questions which will be of general interest to the industry. In answering the third question above, the CJEU held that a product which is developed after the priority date of the basic patent in question as the result of an 'independent inventive step' cannot be considered to be protected by that basic patent for the purposes of Article 3(a) of the SPC Regulation. This is irrespective of whether it falls within the scope of protection conferred by a functional definition.

4 Case C-121/17 *Teva UK Ltd & Ors v Gilead Sciences Inc.* ECLI:EU:C:2018:585

The Court noted that to allow post-filed data into an assessment of whether a product is covered by a patent for the purposes of granting an SPC could unduly benefit the patentee, and that rewarding research that was the subject of a separate invention made after the patent filing undermined the fundamental purpose of the SPC regime. As there is no further explanation of 'independent inventive step', the interpretation of this aspect of the CJEU's judgment may well be the subject of further references in the future.

Santen & new therapeutic applications

Article 3(d) of the SPC Regulation requires that the MA relied on for the purpose of the SPC application is the first MA to place the product on the market as a medicinal product. It was this provision of the SPC Regulation that was in issue in *Santen*.

In brief summary, *Santen* had applied for an SPC for 'ciclosporin for use in the treatment of keratitis', relying on a basic patent for an oil-in-water ophthalmic emulsion of ciclosporin (the active ingredient) and an MA for the medicinal product Ikervis®, which contained ciclosporin. Ikervis is used to treat severe keratitis (which is an inflammation of the cornea).

The French Patent Office refused the SPC on the basis that the MA for Ikervis was not the first MA to place the product on the market. Instead, the earlier MA for Sandimmun® was the first MA for the purpose of the SPC Regulation. Sandimmun also contained the active ingredient ciclosporin but indicated for use in, *inter alia*, preventing the rejection of organ and bone marrow grafts and the treatment of uveitis (which is an inflammation of all or part of the uvea, a different part of the eye from the cornea).

In other words, the MA for Sandimmun concerned a different application of the same active ingredient. Following an appeal from *Santen*, the Paris Court of Appeal referred two questions to the CJEU.

The questions referred considered the scope of the CJEU's judgment in Case C-130/11 (*Neurim*)[5]. By way of reminder, in *Neurim* the CJEU had held that 'the mere existence of an earlier MA obtained for a veterinary medicinal product does not preclude the grant of an SPC for a different application of the same product for which an MA has been granted, provided that that application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the application for the SPC' (emphasis added).

In its first question, the Paris Court of Appeal asked the CJEU to confirm whether a strict or broad interpretation of 'different application' should be adopted. By its second question, the Paris Court of Appeal asked the CJEU to confirm what was meant by 'the limits of protection conferred by the basic patent'.

With reference to Article 1(b) of the SPC Regulation (and the definition of 'product' contained therein), the CJEU held that the fact that an active ingredient (or combination of active ingredients) is used for a new therapeutic application does not confer on it the status of a 'distinct product' if that active ingredient (or combination of active ingredients) has already been used for a different therapeutic application. Consistent with this, the CJEU found that an MA cannot be considered to be the first MA where it covers a new therapeutic application of an active ingredient, or of a combination of active ingredients, and that active ingredient or combination has already been the subject of an MA for a different therapeutic application.

5 Case C-130/11 *Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents* ECLI:EU:C:2012:489

In reaching this conclusion, the CJEU expressly found that 'contrary to what the Court held in paragraph 27 of [Neurim]' there is no need to take into account the limits of protection of the basic patent when identifying the first MA for the product.

Whilst it will be for the referring Court to apply the CJEU's guidance, it seems likely that the French Patent Office's objection to the SPC Application will be maintained. It also seems likely that the CJEU's judgment will have ramifications for other SPCs for new therapeutic uses of known active ingredients (which have already been authorised for use as medicinal products).

What next?

As a number of the recent decisions have related to small molecule products, there is relatively little guidance from the CJEU about how the tests set out in the case law should be applied in the context of biotech products such as antibodies. In this regard, from a UK perspective, it is worth noting the position adopted by Arnold J (as he then was) in *Eli Lilly v Genentech*[6]. In that case, Arnold J held that an antibody was specifically identifiable by the skilled person at the priority date by reference to a claimed function (namely, its binding characteristics). For this purpose, Arnold J also considered that it was irrelevant that the antibody was not created until after the priority date.

Notwithstanding the latest guidance from the CJEU, it seems inevitable that there will be further references regarding Article 3 of the SPC Regulation (albeit not from the UK Courts). However, following the conclusion of the Brexit transition period on 31 December 2020, it is worth noting that any new judgments from the CJEU will no longer be binding on the UK Courts (although they may still be considered). Moreover, at the time of writing, the UK Government is set to implement the proposal that both the English Court of Appeal (and its equivalent in the other UK jurisdictions) and the Supreme Court can depart from retained EU case law (except where a higher Court has previously adopted the CJEU's decisions)[7]. Having said goodbye to 2020 and our membership of the EU, it will be interesting to see how the UK Courts grapple with these issues post Brexit.

6 *Eli Lilly Company & Ors v Genentech, Inc* [2019] EWHC 388 (Pat). For completeness, it is noted that this judgment was handed down before the CJEU's decision in *Royalty Pharma*.

7 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926811/departure-eu-case-law-uk-courts-tribunals-consultation-response.pdf

Uncertain times: Changes to the UK's tax regime

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2020 was an unusual year, and the Budget delivered in March was no exception. For a start, when the Chancellor stepped up to the dispatch box, he was actually presenting a delayed November 2019 Budget and, secondly, it took place at one of the most uncertain times in recent history: the week before the UK's first national lockdown.

Just as Harold Macmillan had proclaimed over a half century earlier, events of the day ultimately shaped the contents of the Budget. Thus, the Budget was focused on addressing the COVID-19 pandemic, a political priority that would remain fixed as the year drew on and various measures were introduced in an effort to prop up the UK economy. It is no surprise that the Budget that should subsequently have taken place in November 2020 was replaced by the delivery of the shorter-term Winter Economy Plan, with the Chancellor explaining that it was 'not the right time to outline long-term plans.'

With the 2021 Budget in March rapidly approaching, now is the time to reflect on what we might see within the Chancellor's red briefcase. Any upcoming tax changes will be aimed at recouping the costs of the pandemic, and so it is unlikely that those changes will be announced until the end is firmly in sight. That being said, there are a few measures looming on the horizon that may impact the biotech industry.

Potential future changes to Capital Gains Tax (CGT)

The Office of Tax Simplification's review of the current CGT tax regime hit the headlines in November 2020 and sparked speculation as to the potential changes coming down the track. However, the Government is yet to release anything confirming that CGT reform is in fact on the cards.

The review found that funds in the region of £14bn could be raised by limiting the existing CGT exemptions and raising the rates. Clearly, this would impact the wealthy, which remains the media's preferred focus.

However, the current CGT regime also includes various reliefs and schemes aimed at encouraging innovation, and so the effects of any reform could have a significant impact on the biotech industry. In the months ahead we could, for example, see a reform of Business Asset Disposal Relief (formerly Entrepreneurs' Relief), which reduces CGT for founders and certain other employee shareholders on the disposal of shares and certain other business assets, from 20% to 10%, subject to various qualifying conditions.

It has already seen a fair amount of reform over recent years, with more stringent conditions introduced and a reduction of the lifetime limit from £10 million to £1 million, and so it is possible that the gradual tapering of the relief could be paving the way for its abolition. However, many are understandably concerned that doing so will act as a deterrent to small business start-ups.

Of course, this is not the only scheme that could be affected by changes to CGT. The Enterprise Investment Scheme (EIS) is one such candidate, which currently provides significant personal tax breaks to UK tax paying individuals who subscribe for shares in EIS qualifying companies, making access to funding much easier for those companies.

One of those tax breaks is a CGT exemption on any gains when the individual sells the EIS shares. If this relief were to be pared back, or even removed, then this may impact investment into small and growing life science companies.

It is also possible that Enterprise Management Incentive (EMI) Schemes, which are used to remunerate employees using share options rather than salaries, could be affected. The tax advantage of a qualifying EMI scheme is that the employee will pay CGT rather than income tax on their gain (or at least a portion of the gain) on the ultimate sale of their shares. Raising CGT rates would therefore significantly limit the benefits of such schemes.

Whilst the Government is yet to set out any actual indicators as to the extent of any reform, it is unlikely that the various CGT reliefs and schemes will be abolished in their entirety, as the impact on growing companies would be too severe. However, if the regime is reformed, then it is likely that at least some of those reliefs and schemes will be impacted.

Exactly how, and to what extent, biotech companies will be affected remains to be seen, but it would be prudent to bear these potential upcoming changes in mind when implementing structures or schemes that are currently attractive due to a CGT benefit, as that benefit may not be available in the near future.

*The biotech market is burgeoning and will only get bigger. The global biotech market's value was expected to reach $727.1bn by 2025. Meanwhile, employment in the sector is expected to **grow by 5%** between 2019 and 2020.*

R&D Tax Credit restrictions

The historic R&D tax credit restriction relating to a company's PAYE and NICs liabilities was removed in 2012, but it is being re-introduced from the 1st April 2021. This will impose a cap on repayment claims of £20,000 plus three times the total PAYE and NICs liabilities of the claiming company.

The purpose of the reintroduction is to target avoidance-driven set ups where a company with little employment or activity in the UK attempts to claim credit under the R&D regime. The £20,000 threshold within the cap was introduced to limit the effect of the restriction on genuine businesses with no avoidance motive (eg. start-ups with few, if any, employees). There will also be an exemption from the cap if employees are creating, preparing to create, or managing intellectual property, and less than 15% of the company's overall R&D is spent with connected persons. This is aimed at companies with low PAYE and NICs liabilities, but who are nevertheless themselves engaged in genuine and substantial R&D. The cap calculation can also include related party PAYE and NICs liabilities attributable to the relevant project.

It is said that tax is one of life's two certainties. At the moment, however, it is still uncertain exactly how the UK's tax regime will be adjusted in light of the COVID-19 pandemic. In what might be called the age of uncertainty, this is one aspect of the political arena that the biotech sector should certainly be keeping a close eye on in the months ahead.

Avoiding bias and increasing diversity in AI and health research

During the COVID-19 pandemic, the notion of different health outcomes for different populations has gained increased profile in the public consciousness, particularly in light of the varying effect of COVID-19 on different community groups.

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The role that bias and discrimination play in this area are important for society to acknowledge and overcome, but few realise that it is not only humans that have these tendencies; our AI creations do too.

As a result, one of the themes of the ICO's recently launched Guidance on AI and Data Protection[1] may surprise those unfamiliar with the workings of AI development: the need to address the risk of bias and discrimination in AI systems, in particular to ensure compliance with the data protection principle of 'fairness'.

Can inanimate drugs and medical devices really be biased?

There is often a misconception that medical devices and AI systems can't produce biased results, as they work using logic and process, rather than being tainted by flawed assumptions based on human error or prejudice.

However, ultimately it is humans that design medical devices, which are tested on human-collected datasets. Similarly, algorithms are also created by humans and many processes forming part of an AI system rely on human input, for example the selection of datasets on which the system is to be trained. Therefore, it is possible for AI systems to provide unbalanced outputs with discriminatory effects, and – by extension – for medical devices to work more effectively for certain sectors of the population (being those sectors whose data has been used for the training). A similar situation arises in drug discovery, where some clinical trials only select participants from limited ethnic groups or backgrounds and the effect of the drug on other social groups is not tested.

In the healthcare sector, fairness is particularly important, as biases can lead to significantly worse health outcomes – potentially for whole communities and, in some cases, potentially the difference between life and death. The Covid pandemic has shone a spotlight on the need for diversity of data in the medical research spheres, as the apparently more severe effect of COVID-19 on individuals from a BAME background (the cause of which, at the time of writing, has not yet been ascertained) has emphasised the negative impact that can occur when sections of society aren't represented in research.

1 https://ico.org.uk/for-organisations/guide-to-data-protection/key-data-protection-themes/guidance-on-ai-and-data-protection/what-do-we-need-to-do-to-ensure-lawfulness-fairness-and-transparency-in-ai-systems/#howshouldweaddress

What's the challenge?

Where AI is trained on data relating only or mainly to one group of people, such as only men or only people from a white ethnic background, the system might not have enough data about other groups to pay attention to any statistically significant relationships that predict certain outcomes for those groups.

For example, heart disease risk factors tend to differ between the sexes[2] but most research on heart disease to date has focused on middle aged men, meaning any AI trained on that data would be much better at identifying the risk factors for a man than a woman. Therefore, a woman's heart disease could go undiagnosed for longer, putting her at higher risk. The same is true that most medical research until recently has focused on symptoms and risk factors for white people with Western lifestyles[3].

Why has this happened? Two theories were discussed at the recent 2020 BIA Bioscience virtual conference[4] ('BIA Conference'). The first is that there is not enough trust between some ethnic minority communities and the research/medical industry. This is thought to be due in part to a lack of people from certain communities working in those industries, due to discrimination and lack of opportunity, and partly due to past health inequalities leading these communities to doubt the efficacy of research and Western medicine for their benefit.

The second theory is that researchers simply haven't recognised the need to diversify the range of participants they include. The desire to control as many variables as possible in a trial also reduces the diversity in trial participants.

Bristows Life Sciences Summit 2021

Following on from the success of our previous Bristows Life Sciences Summit on gene editing, we will be exploring the use of artificial intelligence in the medical sphere in another big debate in November 2021.

Keep an eye out on our website for further details.

Register your interest here.

2 https://www.health.harvard.edu/heart-health/heart-attack-and-stroke-men-vs-women

3 https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001918

4 https://www.bioindustry.org/event-listing/uk-bioscience-forum-2020.html

Currently the majority of genetic data for biomedical studies comes from the Western world, for example from Genomics England, but population studies and biobanks are slowly growing across the world and are available to be incorporated into research.

Data 'silos' can also be damaging and destructive to drug research. They lead to adverse effects for minority groups, as drugs simply aren't tested on members of their communities and/or symptoms aren't as well recognised in those groups. Many drugs are therefore advertised to, and used by, a diverse population, without having been tested on a similarly diverse population. There is a risk from an ethical perspective of creating 'second-class' medical citizens with this approach.

As part of its regulatory priorities in the latter half of 2020, the ICO has been focusing on the risk of bias in AI (and how to prevent this risk from materialising) in its continuing 'Guidance on AI and Data Protection'"[5]. The ICO lists five main contributing factors to bias creation within AI systems:

- Training data may reflect past discrimination (e.g. if it was previously thought that people from a certain ethnic minority didn't suffer from a particular illness because they didn't present symptoms in the same way as white patients);
- Prejudices or bias can occur in the way variables are measured, labelled or aggregated;
- The developers may use biased cultural assumptions;
- Inappropriately defined objectives, which embed assumptions about gender, race or other characteristics;
- The way the model is deployed (e.g. it may use a non-accessibly designed interface, limiting the people that can properly interact with it).

Achieving this change is important from both an efficacy and ethical point of view. For example, only 7% of individuals in the UK Covid vaccine trials were from a Black or Asian ethnicity background,[6] and yet these are communities which appear to be more substantially affected by the illness[7], so a big opportunity is being missed to make sure the vaccine works for all.

Not to mention, from a commercial point of view, drugs which are scalable globally are more profitable, with large markets overseas in continents such as Africa and Asia. As such, it makes good business sense for pharmaceutical and medical device companies to test their products on patients from Asian, African and South American communities, so that they can be confident that the drugs or devices will work across all continents, widening their customer base.

What can be done to decrease bias and increase diversity in health research?

A multi-pronged approach is likely to be the best way to address the causes of non-diverse datasets and the potential for biased or discriminatory outcomes from diagnostic and therapeutic treatments, as the BIA Conference explored.

Building trust

Firstly, any systemic distrust between minority communities and the pharmaceutical/medical device industry can be addressed through the building of long-term links with community focus groups, in particular partnerships with existing community groups. All the better if facilitated by someone who both works in the industry and is from that community.

Providing guidance and education about the rights of individuals under the GDPR should assist with building trust, as organisations can emphasise the robust legal framework in the UK and the EU regulating the use of personal data in such research, combined with increasingly active enforcement by UK and

5 https://ico.org.uk/for-organisations/guide-to-data-protection/key-data-protection-themes/guidance-on-ai-and-data-protection/

6 https://www.nihr.ac.uk/news/people-from-black-asian-and-minority-ethnic-backgrounds-and-the-elderly-encouraged-to-participate-in-vital-COVID-19-vaccine-studies/25870

7 At the date of publication, the cause for this is unclear.

EU supervisory authorities. Alongside this, recruitment processes should be reviewed and adapted to ensure a wider, more diverse pool of candidates is sourced for roles in the industry, so that there is wider representation, which will also over time increase trust within those communities.

Making use of existing diverse datasets

Secondly, the industry can make use of existing datasets from other parts of the world, rather than relying solely on local datasets from populations in Western societies (which for the reasons above are likely to underrepresent some ethnic groups). The data is there, but needs to be advertised and utilised to further increase the range of organisations that can benefit from it.

Companies should also assess datasets likely to be lacking in diversity for the reasons described above and seek to diversify them, by looking for new sources of datasets from other areas of the world and incorporating them into studies. EU & UK research organisations would, as data controllers, still need to comply with the GDPR when processing any personal data within those datasets. The lawful bases relied on would need scrutiny, namely whether they could still rely on legitimate interest under Article 6 and provision of healthcare, public health or scientific research under Article 9.

Using real-time data from use of health apps

In the health tech world, particularly with health apps, it is now easier than ever for medical device companies to receive real-time feedback from users and patients, and to use this knowledge to improve their service offering. For example, if someone feels that a particular feature or question isn't relevant to them or is not something they can relate to, they could flag this and explain why, giving developers a much faster insight into potentially discriminatory processes.

With increasing choice over the apps available to use, it will be those that make patients feel their needs are met and that the company offers personalised, relevant services which are likely to win the greatest share of users. One innovative way to show care about each individual patient is by being able to personalise diagnosis/treatment based on sex, race and other relevant characteristics as relevant/necessary.

Thorough Assessment of AI systems

The ICO has also issued guidance[8] on possible technical methods, including mathematical models sometimes referred to as 'algorithmic fairness', that can be used to reduce the risk of discriminatory outcomes in AI systems. Different solutions are needed for different causes of bias, so analysis will need to be carried out by both technical and compliance teams to assess which one applies best to any particular situation. In addition, some of the methods conflict, so it's a case of assessing which would work best for the particular circumstances, including whether they would impact the statistical accuracy of the data.

It should be noted that 'statistical accuracy', or how often an AI system determines the correct answer when measured against correctly labelled test data, is not the same as 'accuracy' as one of the fundamental data protection principles, which holds that personal data must be accurate and, where necessary, kept up to date[9].

Legal basis

In order to assess whether there is bias or the potential for discriminatory outcomes in AI systems or clinical trials, special category data may need to be processed. Is this possible under the GDPR? As with all processing of personal data, you need to have an appropriate lawful basis under the aforementioned Article 6, and an additional basis under Article 9 for special category data, plus in the UK potentially meeting extra conditions in Schedule 1 of the DPA 2018.

8 https://ico.org.uk/for-organisations/guide-to-data-protection/key-data-protection-themes/guidance-on-ai-and-data-protection/what-do-we-need-to-do-to-ensure-lawfulness-fairness-and-transparency-in-ai-systems/#howshouldweaddress

9 For a more detailed article on the ICO's guidance, please see Bristows' "On The Pulse" online newsletter.

*AI continues to make big strides in the biotech market. **Across all sectors**, AI start-ups raised $73.4bn in 2020, with total VC funding in AI biotech increasing by almost 30%. Xtalpi, the American-Chinese AI assisted drug discovery firm raising $319m in series C funding, typifies recent successes.*

In the health world, data controllers are already processing special category health data – but that is a separate consideration from data about race and other characteristics for the purpose of ensuring the data used to train the AI system is not going to result in biased decisions or outputs produced. For this purpose, data controllers can rely on the research ground under Article 9(2)(j) if they can meet the extra requirements under article 89, or the substantial public interest condition under article 9(2)(g).

The future for AI, post-Covid

In the post-Covid world, a focus on fair, balanced datasets in the biotech sphere is likely to become more commonplace as companies, public bodies and the general public have been awakened to the issues that arise when certain groups or communities are left out of research and trials. At the same time, new entrants into the market and some established ones are increasingly run by a generation which is very aware of the need to break down discriminatory practices in society and is more open to asking new questions and putting new processes in place to tackle this issue.

An increase in targeted technological investment will allow developments such as federated technologies, which can allow forensic analysis of the data where it is stored, without having to move it. This allows data controllers to avoid the transfer of data, with the added expenses, storage space and regulatory requirements that such movement incurs.

Developments in technology also allow companies to start interacting with patients in new ways, which might be easier and more accessible for them, such as phone messaging or video calls. This in turn should open up communications with new communities. Companies can also now collect feedback much more easily online, quickly and efficiently understanding what isn't working for certain groups of patients. These findings can then be scaled up for populations. However, the full benefits of technology will only be realised if companies take the time and effort to invest in providing privacy and security reassurance to patients, in particular through emphasising the legal rights of data subjects and the obligations on data controllers and processors through data privacy laws.

It remains to be seen whether regulators will take these issues into their own hands. The FDA is arguably the most vocal regulator on this point and has recently published guidance[10] about recruiting diverse populations for clinical trials. The ICO has issued specific guidance on avoiding bias in AI systems, and this issue is likely to become more pressing over the coming years.

It could be that regulators now start to move from the 'carrot' of guidance to the 'stick' of regulation to combat bias in AI systems, and the more successful companies are likely to be those ahead of the curve on this issue. Success will come from being conscious of the possibility of bias, even in our machines.

11 https://www.fda.gov/media/127712/download

Spin-outs: What will 2021 hold for UK universities?

In October 2020, Oxford University spun out its 200th company. The launch of PhishAhr – an augmented reality app designed to combat fake website 'phishing' scams – capped a successful year for Britain's oldest university, having secured over £880m in external funding, eclipsing previous records.

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Nick Cross
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Well represented within the 200-strong list of companies are the life sciences; the university proudly declared how three of its offspring were developing ventilator and testing technologies to help tackle COVID-19. But though the pandemic may have spurred investor interest in life sciences to an extent, in truth, the university life science spin-out was burgeoning even beforehand. After all, whilst it took Oxford 55 years to spin out its first 100 companies, the second hundred were spun out in just six. At the time of writing, the Vice Chancellor is already publicly anticipating the 300th.

The 'Golden Triangle'

If Oxford's spin-outs reflect the essential health of the sector – UK universities raising almost £1.25bn in 2019 alone – it also betrays another important trend: the predominance of a 'Golden Triangle' of institutions. Oxford, Cambridge and the London Universities, such as UCL, KCL and Imperial, lead the pack in life sciences. Such a situation is inevitable. The research facilities and capital reserves of these universities, which boast a combined endowment of over £14bn, means their preeminence will likely be maintained in the coming years.

*In October 2020, **Oxford University** spun out its 200th company. Having gone from 100 to 200 such companies in six years, the Vice Chancellor is already predicting the 300th.*

Let's also not forget that these institutions simply have more academics. Cambridge, for example, is made up of over 100 departments, faculties, schools and institutes. More research staff means more ideas capital, supported by incredibly deep pockets.

That's not to say there haven't been efforts to encourage spin-outs from across the UK's wider academic institutions. The Vice Chancellor of Keele, for instance, published a report in 2017 urging the Government to offer greater guidance to help all universities spin out companies. But though this would benefit the UK market, there is no one-size-fits-all solution to easily implement and it is unlikely the Golden Triangle will be seriously challenged in the near future. And it is here that investors' eyes will remain trained.

The stealth company

One of the trends changing the sector as we enter 2021 will not actually be immediately visible. Indeed, the last few years have seen the rise of the stealth spin-out: companies that keep their growth and funding tightly under wraps until emerging almost from nowhere. The only indications of the existence of such companies are typically several job adverts attached to a minimalist website homepage. Regularly checking job listings, then, might prove fruitful for the savvy investor.

For the most part, the desire to attract minimal attention early on is driven by practical business considerations. Making too much noise too soon risks alerting competitors to nascent technology and its financial viability, which would be a highly dangerous strategy if the right IP protections are not already in place.

Crucially, with the media spotlight firmly on the life sciences sector, we can only expect stealth companies to continue to grow, albeit covertly, in 2021.

Where's the money?

This last point is critical, albeit easily misinterpreted: though COVID-19 has shone a spotlight on the sector, the spike in investment activity has not been commensurate with the increased publicity. This is not to disparage the sector; it's simply the case that the sector was blossoming before the pandemic. Indeed, 333 UK companies in the life sciences sector raised equity in 2019 whilst deal activity increased by 5%. The success stories of the last few years are typified by Autolus, Freeline and Orchard Therapeutics, amongst others, all of which quickly reached NASDAQ.

Inevitably, COVID-19 will throw up opportunities for investors, but (at the time of writing) with vaccines seemingly looming into reality, other areas will also offer rich pickings. Diagnostic and gene therapy spin-outs will likely attract significant investor attention in 2021. More broadly, we may also see increased activity at the intersection of tech and life sciences, not least when it comes to diagnostic technologies.

There is also likely to be an increased activity around university and partner funds, which see the institutions entering into strategic arrangements with chosen investors or fund managers, often providing for some type of priority access to technologies being spun-out from that institution. Oxford Sciences Innovation (OSI), which has a long-standing and successful track record of partnering with Oxford University, is emblematic in this regard; and with 2020 witnessing the launch of UCL's second tech fund, we can only expect such activity to increase in 2021. What's more, we may even see a growth, if not a continuation, in institutions themselves investing into life science funds.

The growth in university and partner funds, stealth companies and the spin-out 'engine' of the UK's golden triangle all suggest that 2021 will be a strong year for UK spin-outs, but given the pandemic disruption only time will tell how the market will ultimately evolve.

A growing trend of smaller, early-stage investments in UK life sciences

Amidst the pandemic disruption and market highs of the life sciences sector in 2020, one par-ticularly interesting trend was the growing volume of seed investment funding in UK-based life sciences companies, which looks set to have a material effect on the sector throughout 2021.

Nick Cross
Associate

As its name suggests, seed investment refers to when a small amount of capital is invested into an innovative start-up or spin-out earlier in its product development than usual investment strategies would advise. Typical of the venture arms of larger pharmaceuticals, or smaller entities active at a commercialisation level in the sector, this seed capital isn't necessarily intended to generate returns, at least not immediately.

A behind-the-scenes reveal

Instead, seed investment allows strategic investors to get a first look at innovations and technology ahead of the lengthy and capital-intensive timescales typical of the sector.

Seed investors often offer deal terms that include enhanced information rights or rights of first refusal for new products or technology in return for their investment – providing the much-needed capital to benefit smaller labs and researchers while they themselves are kept abreast of the most cutting-edge developments. The arrangement is mutually beneficial: pioneers get vital funds to bring products to market, and larger companies are able to tap into the innovative, trail-blazing work of cutting-edge start-ups.

As a trend that pre-dates the pandemic – alongside the rising interest of private equity in the life sciences sector, the growth in collaboration and the increased importance of the spin-out – an increasing volume of seed investment is a sign that investment into the life sciences sector is becoming ever-more sophisticated.

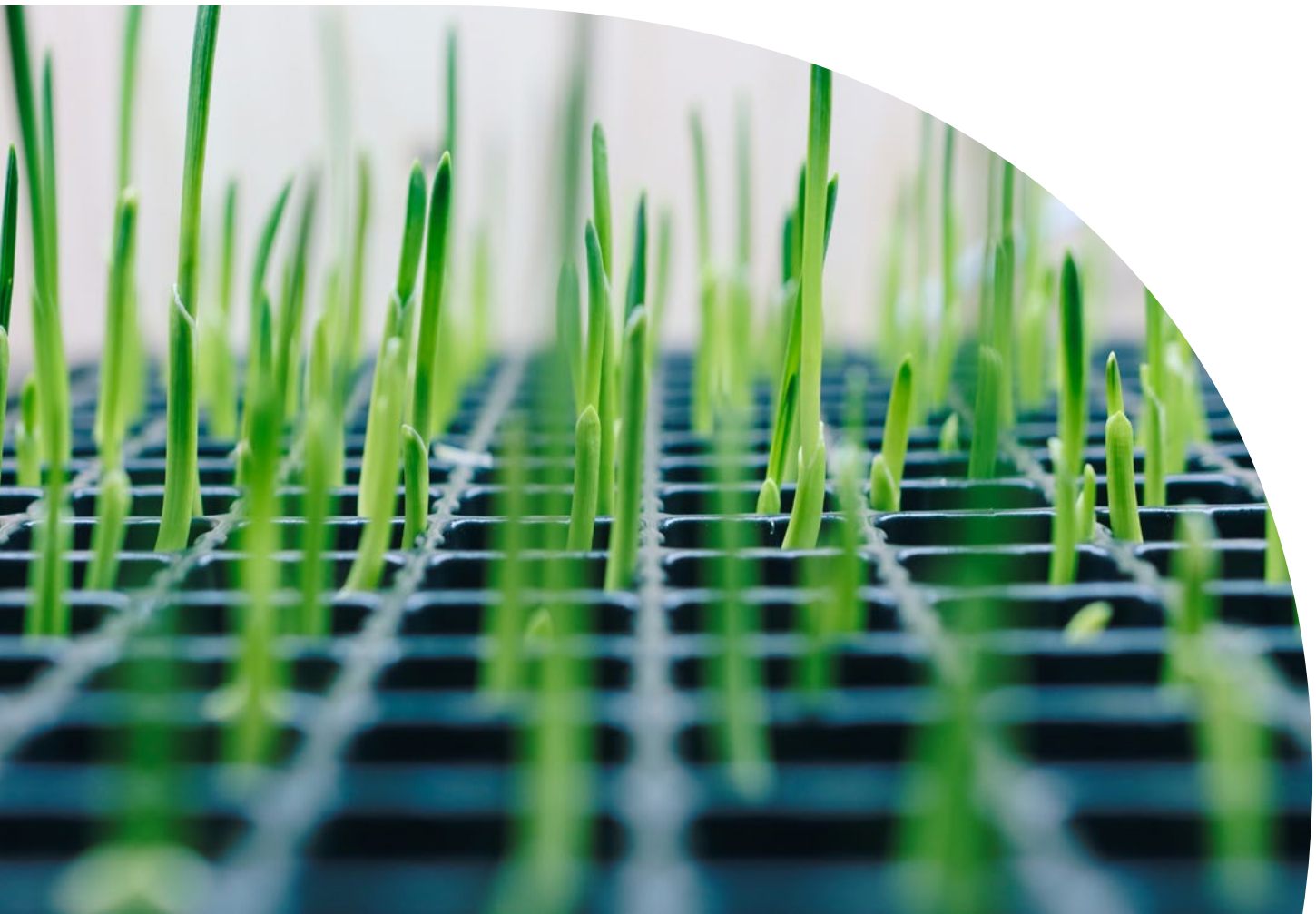
Looking for a bullseye

Particular targets for seed investment are spin-outs from larger companies or universities, both in the largest life sciences market – the US – or in the UK, which sits comfortably as the second largest market in the West. These market positions are indeed largely thanks to the strong university medical research in both nations, whether based on the US life sciences breadbasket of Massachusetts, or the UK's 'Golden Triangle' between Oxford, Cambridge and London.

While seed investor interest in the US and UK seems set to remain, we are seeing changes in terms of the areas of technology attracting the most attention. 2019 saw all eyes on the fields of cell and gene therapies, unsurprising given the ongoing excitement over CRISPR gene editing that largely defined the decade. However, 2020 begun as the decade of the COVID-19 pandemic and, accordingly, interest has inevitably shifted toward medical devices and diagnostics.

Similar trends have emerged alongside the rise of seed investment, from the life sciences accelerators launched by Merck and the Frances Crick Institute, to the IPO boom of 2019-20. Innovation is at an all-time high and, from the first incorporation to listing publicly, companies now have greater options in where to find capital and guidance.

As a result of their scientific focus, smaller biotechnology companies can react nimbly to evolving science in product development. Acquisition and partnership in this segment of the market allows the larger players to capitalise on this agility, while providing a springboard for many a start-up or spin-off's trajectory. We look forward to seeing it continue into 2021.



About us

Bristows has one of the most highly-regarded multi-disciplinary life science legal practices in the world.

We have a true cross-disciplinary team in this space encompassing our renowned IP practice, regulatory, competition, transactional, dispute resolution, IT and data protection teams. The strength of each individual practice complements the others to provide a fully integrated and comprehensive service.

Our life sciences specialists - many with backgrounds in biology, chemistry, biochemistry, genetics and neuroscience - work with leading clients across the private, public and academic sectors.

We pride ourselves on the breadth of our client base in the sector and actively seek to advise clients from the different key participants making up the life sciences eco-system. As such we act for global pharma, specialist investors, growing biotech and medtech companies, universities and research institutes, specialist service providers and government funded bodies. Our clients also include tech companies now entering the sector as convergence takes hold.

We believe that these different perspectives help us to best advise our clients and give us true expertise in relation to the sector and where it is heading.

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