

Biotech Review

Issue 7



Bristows

The information contained in this document is intended for general guidance only. If you would like further information on any subject covered by this Bulletin, please email Greg Bacon (gregory.bacon@bristows.com), Xisca Borrás (xisca.borras@bristows.com) or the Bristows lawyer with whom you normally deal. Alternatively, telephone on + 44 20 7400 8000.

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Biotech

figures 2019

In worldwide sales, there has been a rapid increase in the share of top 100 products for biotech.

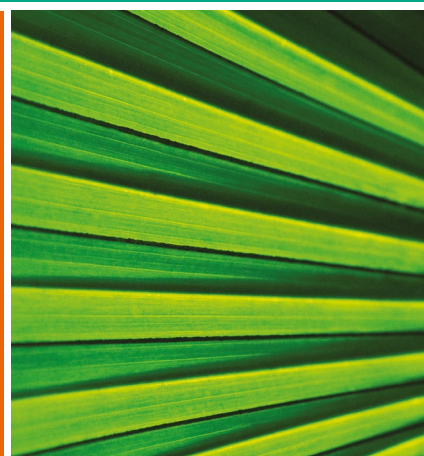
In 2018, 53 percent were biotech products as compared with 34 percent in 2010. The forecast period to 2024 expects a 50/50 split.

Deloitte,
[2020 Global life sciences outlook](#)

On the IPO front, globally, the biotech sector had its second-best year ever.

Indeed, the sums raised globally at IPO in 2018 and 2019 combined account for about a third to the total raised by the industry since the turn of the century.

UK BioIndustry Association (BIA),
[Global and growing, UK biotech financing](#)



The UK biotech sector raised £1.3 billion in 2019.

The total is the third highest year recorded by the trade association and since 2012 investment has increased by over 400%

UK BioIndustry Association (BIA),
[Global and growing, UK biotech financing](#)

In the past five years globally, biotechs have raised more than \$140bn in equity.

Consequently, companies have the resources to translate ground-breaking science.

UK BioIndustry Association (BIA),
[Global and growing, UK biotech financing](#)



There are now 1257 Biotech companies in the UK, this is up 2% from last year.

Other Services and Suppliers, Diagnostics and Analytical Services and Therapeutics make up the majority at 23.6%, 20.7% and 16.5%

[UK Biotech Database](#)

Welcome to the latest edition of Bristows' Biotech Review

Dear readers,

We have included some of the most important and influential developments in the biotech sector in 2019, and also look forward to those matters likely to affect the industry in the short to medium-term future.

A focus for this edition of our Biotech Review is gene editing. 2019 saw Bristows facilitate a life sciences debate on the implications of human genome editing ("The quest for the perfect human...?").

Gene therapy not only brings significant technical advances to the clinic, but can also raise ethical concerns, particularly where germline therapy is concerned, as well as the potential for novel payment arrangements reflecting the lifetime gains that may be achieved after a single treatment.

Whilst gene therapy may be the future, monoclonal antibody products continue to lead the way in the present, both in terms of market share and sales, but also in relation disputes to between competitors. We have included updates on a number of originator/biosimilar and patentee/originator disputes in this space, as well as a smattering of other topics across the board that will be of interest to the biotech sector.

As always, we encourage you to send any feedback you might have so that future editions contain even more of what you would like to receive. Please also let us know if you would like to read more information about any of the topics featured in this edition.

Please note:

The contents of this edition of the Biotech Review were drafted prior to the full impact of the COVID-19 pandemic and the authorities' responses to the disease in Spring 2020. They do not therefore reflect the significant impact that the disease is having on the life sciences industry, health services, the wider economy and society more generally. No doubt the next edition of our Biotech Review will have a very different focus. We hope that all readers and their friends and family are keeping well during these difficult times.



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Greg is an experienced IP lawyer with a particular focus on patent litigation in the life sciences sector.

His extensive scientific background gives him a valuable understanding of technical issues that can underlie IP matters, particularly in the life sciences field. He has advised and represented clients on small molecule pharmaceuticals, biologics (originators and biosimilars), medical devices (hardware and software), as well as in the cosmetics, chemicals, technology, shipping and online publishing sectors.

Greg has represented clients in many cases before both the English High Court and Court of Appeal. In addition, Greg has extensive experience of strategic multinational litigation in multiple jurisdictions, including at the EPO, through global pharmaceutical product coordination projects for many clients.

Dosage regimen research; is it worth it?



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A recent UK Supreme Court decision calls into question whether biotech companies should continue to invest in dosage regime research. Optimising dosing regimens is undoubtedly beneficial to patients as it can improve efficacy profiles and reduce side effects. However, the required pre-clinical and clinical research represents a large capital investment which the availability of patent rights helps to justify. The Supreme Court decision in *Actavis v ICOS Corporation*¹ addresses the availability of patent rights for dosage regimens and therefore also the value of existing patents that protect such research.

The Court's decision

The drug in question was tadalafil, a bestselling treatment for erectile dysfunction. Tadalafil is authorised for use by patients 'on demand' where it is administered a period of time ahead of its effects being desired or, alternatively, at a lower daily dose which provides all day coverage. The Court accepted that Eli Lilly had conducted extensive research into ascertaining the lowest effective dose of tadalafil which could be used for daily dosing by patients, and this result was not predictable in advance. However, the Supreme Court found that Eli Lilly's discovery was a result of "...pre-clinical and clinical tests [that] involved familiar and routine procedures and normally progressed to the discovery of the dose-response relationship...". The Court therefore found the patent invalid and revoked the right.

Why does it affect me?

In reaching its decision the Supreme Court considered the patent protection which is provided for dosage regimens more generally so is equally applicable to the biotechnology industry. In particular, the Court reaffirmed that while there was no reason why patents should not

be granted for the results of new and innovative research into dosage regimens, these criteria are typically not met when determining appropriate dosage regimens. This was because the target of such research is largely pre-determined.

What can I do?

At first glance patents protecting dosage regimens, especially those resulting from standard pre-clinical and clinical testing required to bring a product to market, are vulnerable to being rejected or revoked and will be valued accordingly. However, this may not always hold true. In particular:

- The Supreme Court confirmed that the burden and the cost of research is a relevant factor when considering whether a patent right is available. The courts should take into account that from a policy perspective it is important to facilitate expensive pharmaceutical research.
- A distinction can be drawn for research which is not routine or where the target of the research is not pre-determined. This may encompass, for example, additional research on established medicines already on the market or where the research is being conducted on a drug which, without proprietary information, would seem commercially unviable.
- It is sometimes possible to file additional patent rights or amend existing patent rights so that issues with the patentability of dosage regimens can be avoided or mitigated. However this is best assessed on a case-by-case basis.

¹ *Actavis Group PTC EHF and others v ICOS Corporation and another* [2019] UKSC 15 – Bristows' full legal analysis of this decision can be found at <http://patentblogklaweriplaw.com/2019/03/27/the-supreme-court-decision-in-actavis-v-icos/>

Mammoth judgment on IL-17A/F antibodies leads to patent revocation and brief SPC excursion to the CJEU



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On 1 March 2019, Mr Justice Arnold (as he then was) handed down judgment following a 12 day trial in the Patents Court involving Eli Lilly and Genentech. The litigation related to anti-IL-17 antibodies, which can be used to treat auto-immune diseases such as psoriasis and ankylosing spondylitis. In addition to the patent dispute, the case gave rise to interesting SPC issues, in particular third party MA SPC applications. In the judge's own words, it was *"one of the most complex patent cases"* he had ever tried and had potentially far-reaching consequences for the pharmaceutical industry.

The action concerned Genentech's European Patent (UK) No. 1 641 822 ("EP822"). EP822 claimed an antibody *"which specifically binds to an isolated IL-17A/F heterodimeric complex..."*, and the use of that antibody to treat psoriasis and rheumatoid arthritis (RA) via EPC 2000 and Swiss-type claims. IL-17A/F is a dimer of IL-17A and IL-17F monomers. It is now known that various forms of the dimer (IL-17A/A, IL-17A/F and IL-17F/F) have been seen to be elevated at different stages of autoimmune disease and inflammation. Their precise roles, however, have not yet been elucidated. Notably, Genentech has not commercialised an anti-IL-17A/F antibody.

Eli Lilly ("Lilly") had independently developed ixekizumab (trade name: Taltz®). Ixekizumab is an antibody that binds to the IL-17A/A homodimer and the IL-17A/F heterodimer with equal affinity and is marketed for the treatment of psoriasis and psoriatic arthritis. In July 2017, Lilly sought a declaration of non-infringement in respect of ixekizumab and EP822, as well applying to revoke the patent. Genentech counterclaimed for infringement.

In addition to the patent dispute, Genentech had filed an SPC application based on EP822 and Lilly's MA for Taltz®. Lilly objected to this application and sought a declaration that such an SPC would be contrary to Article 3(a) of Regulation (EC) No 469/2009 (the "SPC Regulation"), as Taltz® was not a product protected by EP822, nor was the Taltz® MA a valid authorisation for the purposes of Articles 3(b) or 3(d) of the SPC Regulation on the basis that Lilly had not consented to Genentech applying for an SPC based on the Taltz® MA.

Patent Decision¹

Construction

A fundamental issue in the case related to the construction of claim 1 which, as proposed to be amended, claimed:

"An isolated antibody which specifically binds to an isolated IL-17A/F heterodimeric complex and which inhibits the activity of the IL-17A/F heterodimeric complex to induce the production of IL-8 and IL-6, wherein the isolated IL-17A/F heterodimeric complex comprises SEQ ID NO:3 and SEQ ID NO:4, without their associated signal peptides, and further comprises two interchain disulphide linkages between SEQ ID NO:3 and SEQ ID NO:4; and wherein the antibody is either man or humanized."

In particular, there was disagreement over what "specifically binds" means. Lilly argued that an antibody that "specifically binds" to IL-17A/F should do so to the exclusion of all other targets (including, for example, the IL-17A/A homodimer). Genentech maintained that such an antibody should bind to IL-17A/F in a manner that was not non-specific (i.e. by "sticky" adherence alone). The judge found in favour of Genentech's broader construction.

Added Matter

Prior to the UK litigation, EP822 had been revoked by the Opposition Division for added matter grounds (the decision of which was still, at the time of writing, under appeal before the EPO's Technical Board of Appeal). During the course of the UK proceedings, Genentech applied to amend its claims and similar added matter objections were raised by Lilly. Arnold J respectfully disagreed with the approach adopted by the Opposition Division and allowed the amendments, demonstrating perhaps the English courts' more lenient and less rigid approach when it comes to added matter. The Technical Board of Appeal has since upheld the decision of the Opposition Division on added matter.

Obviousness and Novelty

On novelty and obviousness, Lilly focussed their efforts on two streams of prior art: (i) IL-17A/F prior art; and (ii) IL-17A/A prior art. In the former category, US patent 6,043,344 was found to be an enabling disclosure of an IL-17A/F heterodimer. At the priority date, Arnold J held

that it would have been obvious to the skilled person to produce a humanised antibody to IL-17A/F, rendering the antibody per se claims obvious. Furthermore, at that time, IL-17A/A was known to be a key factor in the pathogenesis of RA. On the back of the US patent, the skilled person would have considered it reasonably likely that IL-17A/F existed in nature and thus it would be a promising target for RA, which would lead them to conduct tests and trials in humans. The medical use claims, insofar as they related to RA, were thus also obvious.

Turning to the IL-17A/A prior art, it was common ground that IL-17A/A itself and IL-17A/A antibodies were known at the priority date. Lilly argued that working the IL-17A/A prior art would inevitably result in antibodies that bind to IL-17A/F, providing evidence that no such IL-17A/A-only antibody existed in reality, nor could it in theory. To support its invalidity case, Lilly also carried out experiments to characterise murine antibodies to IL-17A/A (murine antibodies having been described in the prior article), humanise them and characterise the results. One of the experimental protocols proposed by Lilly's expert required the use of active recombinant human IL-17A/A to immunise mice to generate hybridomas. However, section 5C of the Animals (Scientific Procedures) Act 1986 does not permit experiments on animals for the purposes of patent litigation. Lilly thus relied on three particular murine antibodies to IL-17A/A that had already been generated in the 90s for the purposes of its experiments, instead of generating its own panel of antibodies for humanisation. Whilst Arnold J held that it was not proven to be inevitable that all IL-17A/A antibodies would bind to IL-17A/F, he accepted the premise of the experiments and found it to be highly probable that they would and thus the antibody claims, and medical use claims directed towards RA, were obvious.

Lack of plausibility insufficiency

Applying the test set out by the Supreme Court in *Warner-Lambert*², Arnold J stated that the correct question to ask was whether the skilled person would consider it plausible that an IL-17A/F antibody would have a discernible therapeutic effect on psoriasis. It would not be enough that IL-17A/F was a potential target for psoriasis therapy and deserving of further research to determine the efficacy of an IL-17A/F antibody.

Arnold J found that the claim to psoriasis was speculative and not plausible. He based this decision on the following factors: (i) the absence of experimental data regarding IL-17A/F and psoriasis in the patent; (ii) the lack of discussion regarding IL-17A/F in psoriasis in the prior art; (iii) the limited support for IL-17A/A (let alone IL-17A/F) having a pathogenic role in psoriasis; (iv) the patent indicated that IL-17A/F was less potent than IL-17A/A; and (v) the specification claimed efficacy against a broad list of conditions (for which it was implausible that an anti-IL-17A/F antibody would be effective against all of them).

Infringement

In light of the broad construction of “specifically binds”, Arnold J found that ixekizumab, which binds to IL-17A/F and IL-17A/A with equal affinity, infringed the antibody per se claims. Arnold J also considered infringement of the claims on the basis of the narrower proposed construction, which he had rejected. Applying the doctrine of equivalents, he found that the variant (an antibody that inhibited IL-17A/A as well as IL-17A/F) would achieve substantially the same result in substantially the same way, as both IL-17A/A and IL-17A/F were pro-inflammatory cytokines involved in psoriasis. He held that this would be obvious to the skilled person at the priority date and there was nothing in the patent to indicate that it was essential for antibodies to bind to IL-17A/F only. Thus, even on a narrow construction, ixekizumab would infringe the antibody claims, had they been valid.

Looking next to the medical use claims, Arnold J held that ixekizumab was essential for putting the invention into effect and Lilly would be supplying the product knowing that the users would intend to treat psoriasis with ixekizumab. These claims (to the extent they covered use for treatment of psoriasis) would thus be infringed, save for the invalidity findings.

In summary, the antibody claims were found to be obvious over both the IL-17A/F and IL-17A/A prior art, as were the RA medical use claims. The psoriasis medical use claims were insufficient for lack of plausibility. Had they claims been valid however, they would have been infringed by ixekizumab.

SPC Decision⁵

As noted above, Lilly challenged Genentech's SPC application on two grounds: (1) ixekizumab was not protected by EP822 for the purposes of Article 3(a) of the SPC Regulation; and (2) Lilly's MA for Taltz® was not the correct MA pursuant to Articles 3(b) and/or 3(d) of the SPC Regulation (the “Third Party MA Issue”).

Article 3(a)

Applying the test as described by the CJEU in *Teva v Gilead Sciences*⁴, Arnold J found that ixekizumab necessarily falls under the invention of the patent, as it is an antibody as claimed in claim 1 and embodies the technical contribution of the claim. Turning to the second limb of the test, he held that ixekizumab would be specifically identifiable by the skilled person at the priority date by reference to the functions in claim 1, i.e. it specifically binds to IL-17A/F.

Notably, Arnold J stated that it was irrelevant for the purpose of both limbs of the test that ixekizumab was not created until after the priority date. Had the patent been valid, it would have protected ixekizumab.

Third Party MA Issue

Lilly relied on comments from the Court of Justice of the European Union (CJEU) and national case law to support its argument that the SPC Regulation was intended to compensate innovators for the erosion of their patent term caused by delays incurred by the regulatory approval process. Genentech countered that it was implicit from the case law (namely *Biogen v SmithKline Beecham Biologicals*⁵) that the basic patent and MA may be held by unconnected parties. It alleged that Lilly was attempting to read words into the SPC Regulation and it further noted that Regulation No 1610/96/EC (the equivalent SPC Regulation governing plant protection products) demonstrated that third party MA SPCs are permissible.

Whilst Arnold J saw the merit of Lilly's policy arguments, he could not dismiss Genentech's contentions. He therefore found that the law was not *acte clair* and referred the following question to the CJEU:

"Does the SPC Regulation preclude the grant of an SPC to the proprietor of a basic patent in respect of a product which is the subject of a marketing authorisation held by a third party without that party's consent?"

It was notable that Arnold J referred this question despite finding that EP822 was invalid, thus rendering the SPC dispute academic, at least pending the outcome of any appeal. He justified the referral on three grounds. First, it was likely that Genentech would appeal the decision and, given that the UK's departure from the EU ('Brexit') was due to occur on 29 March 2019 (at the time of judgment), it was possible that the Court of Appeal would no longer have jurisdiction to make referrals. Second, Genentech had filed SPC applications based on EP822 and Lilly's MA in other EU Member States. An EU-wide answer would thus assist the parties. Third, it was in the interests of the wider pharmaceutical industry to settle the Third Party MA Issue. This topic had been hotly debated for years and its resolution would be welcomed.

The CJEU Decision

After Arnold J made the reference to the CJEU by Order on 4 March 2019, the UK's exit from the European Union on 29 March 2019 was postponed. Nevertheless, Arnold J's reference was in the queue for the CJEU's consideration, much to the interest of pharmaceutical companies and SPC enthusiasts throughout Europe.

On 5 September 2019, the CJEU issued an Order declaring that the reference was manifestly inadmissible⁶. The CJEU noted that a reference is to be rejected where the problem is hypothetical, which includes the circumstance where the basic patent had been held to be invalid. Notwithstanding the hypothetical nature of the dispute, the CJEU considered that the grounds put forward by Arnold J were not capable of justifying

the reference. First, the grounds were based on several hypothetical premises: (i) that Genentech would file the appeal; (ii) that the Court of Appeal would overturn the first instance decision; and (iii) that the Court of Appeal would feel it necessary to make a referral. In relation to the then-impending Brexit date of 31 October 2019 (which was again extended), the CJEU remarked that the UK's notice of intention to withdraw from the European Union was just that: a mere notification. It is not an actual withdrawal. Until that date, EU law applies and any Court of a Member State may refer a question to the CJEU. In the CJEU's view, the fact that there were parallel disputes in other Member States, and that the wider pharmaceutical industry had an interest in seeing the issue resolved, was irrelevant to the question of admissibility.

To be Continued

This case has been interesting for IP practitioners to follow, not least for Arnold J's application of the relatively newly-minted *Warner Lambert* insufficiency test and the subject matter of the litigation itself – biologics. Another fascinating aspect of this litigation has been its foray into the world of SPCs and the murky arena of Brexit. The UK Court's attempt to resolve the Third Party MA Issue was welcomed by practitioners, and the CJEU's reluctance to engage on the topic has certainly disappointed some, although of course others will be pleased with the outcome. As a wider takeaway, it is apparent that the CJEU will not be influenced by the time-pressure of Brexit when it comes to considering referrals, although this may now change with the subsequent confirmation that the UK has indeed left the EU on 31 January 2020.

Whilst the Third Party MA Issue has been seemingly extinguished by the CJEU, the UK litigation rumbles on. Genentech appealed Arnold J's judgment which, at the time of writing, had been listed to be heard in January 2021. Following on from the CJEU's dismissal of the referral on the Third Party MA Issue, Lilly applied to the UK Patents Court seeking a reasoned judgment on the issue as no decision had been given in the SPC action. The court refused to provide judgment as the patent had been held invalid - if the judge were to provide a reasoned decision, it would only be *obiter*. Further, the judge noted that Lilly had other opportunities to raise the Third Party MA Issue, for example in the main appeal, as it is only a point of law, as well as in further proceedings between the parties concerning a divisional patent which are currently pending before the Patents Court.

¹ *Eli Lilly and Company & Ors v Genentech Inc* [2019] EWHC 387 (Pat)

² *Warner-Lambert v Generics (UK) (t/a Mylan)* [2018] UKSC 56

³ *Eli Lilly v Genentech* [2019] EWHC 388 (Pat)

⁴ Case C-121/17 *Teva v Gilead* EU:C:2018:585

⁵ Case C-181/95 *Biogen v SmithKline Beecham Biologicals* EU:C:1997:32

⁶ Case C-239/19 *Eli Lilly & Co v Genentech* EU:C:2019:68

Pfizer v Hoffman-La Roche – evading Arrow declarations



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Arrow declarations are a relatively newly-developed form of relief that allow a party to gain commercial certainty against pending patent applications, often for the purpose of clearing the way prior to generic or biosimilar launch. The possible existence of the jurisdiction to grant such negative declarations in the UK was first floated a decade ago in *Arrow v Merck* before the Court of Appeal finally confirmed their availability in *FKB v AbbVie* in 2017. In the case of *Pfizer v Hoffman-La Roche*, Birss J has further clarified the extent of the court's discretion to grant these negative declarations. In summary, he found that the court's power to grant *Arrow* declarations is wide, but should be limited to the extent that it will serve a useful purpose within the UK.

Arrow declarations to date

In the landmark case of *Arrow v Merck*¹, Kitchin J (as he then was) first recognised that the English courts might have jurisdiction to grant eponymous *Arrow* declarations, although the court did not have to decide the matter as the case settled before trial. As readers may be aware, *Arrow* declarations are associated with the so-called *Gillette* defence². In essence, this provides an alleged infringer with an absolute defence during patent infringement proceedings on the basis that its product or process was disclosed in the prior art or is an obvious modification, and as such could not therefore infringe any valid patent claim, regardless of the form or scope of those claims. In an *Arrow* declaration case, the applicant therefore seeks a declaration that its product or process would have been anticipated and/or obvious as at the priority date of the pending patent application(s) of concern. If granted, the declaration therefore allows the applicant to launch its biosimilar product (by way of example) without the threat of future infringement action based on the pending patent applications.

As mentioned above, the Court of Appeal finally confirmed that the jurisdiction to grant such declarations existed in the seminal case of *FKB v AbbVie*³. In the Court of Appeal, Floyd LJ held that there was no issue of principle against the granting of *Arrow* declarations in appropriate cases, and that “*whether such a declaration is justified depends on whether a sufficient case can be made for the exercise of the court’s discretion in accordance with established principles*”⁴. The Court of Appeal also approved the approach proposed by Neuberger J in *Financial Services Authority v Rourke*⁵ for determining whether to grant discretionary negative declaratory relief, in that the court should take into account: “*justice to the claimant, justice to the defendant, whether the declaration would serve a useful purpose and whether there are any other special reasons why or why not the court should grant the declaration*”.

Carr J provided further guidance in his judgment following trial in the same case (*FKB v AbbVie*⁶), in which he granted the first ever *Arrow* declarations, this time in relation to biosimilar adalimumab. As we will see in the *Pfizer v Roche* case analysis, the court's interpretation of what would serve a useful purpose appears to be wide and places great emphasis on the existence of an impact on the UK market.

Background to the present case

Pfizer brought a claim for *Arrow* declarations in relation to its biosimilar VEGF monoclonal antibody medicinal product (bevacizumab), which is for treatment of various cancers in combination with other drugs. This was in the context of Roche's originator bevacizumab product, Avastin, which is the subject of an SPC expiring in June 2020, for which the basic patent is to bevacizumab itself. Pfizer's stated intention is to launch its product following SPC expiry. However, Roche had further patents and patent applications to combinations of bevacizumab with other known cancer drugs for use in treating various types of cancers, including two forms of cancer included in the summary of product characteristics in the marketing authorisation for Avastin. Hence Pfizer's claim for *Arrow* declaratory relief prior to product launch.

By the time of the trial however, Roche had de-designated the UK from all pending applications, either before or shortly after commencement of the proceedings, and no longer had any granted UK patents, in the concerned patent families. Nevertheless, Pfizer contended that *Arrow* declarations would still be useful to establish certainty in the UK market considering that it planned on supplying its biosimilar product from Belgium, which was not de-designated from the pending European patent applications. As a result, it was claimed that the supply chain to the UK would be disturbed, should Roche initiate and succeed in any infringement action before Belgium courts, including by way of an application for a preliminary injunction.

In response Roche submitted that the Court did not have jurisdiction over the issue as it had de-designated the UK from all pending patent applications and thus abandoned any future relevant rights regarding Avastin, whereas Pfizer contended that the Court's discretion to grant an *Arrow* declaration was “almost unfettered” and could apply even in these circumstances. The claimant thus took the position that the useful purpose criteria should be interpreted widely to encompass any benefit such declaration could grant, including the use of a favourable UK judgment before foreign courts.

Shielding conduct

At a high level, there were two issues at trial: (i) the technical issues regarding novelty or obviousness of the use of the various bevacizumab combinations for the relevant indications; and (ii) whether the court should examine the technical issues in detail if it had decided that an *Arrow* declaration would not be granted.

Roche declined to respond to the technical allegations brought by Pfizer (other than one point on priority). Therefore Pfizer was the only party to present written expert evidence on these issues, and Roche chose not to cross-examine Pfizer's experts. On the material before him, Birss J was of the view that there was a compelling case in favour of a *Gillette* defence. Although the judge decided not to go further and decide the various technical issues, he stated that it was nevertheless relevant to examine the apparent merit of the technical case as it might help explain the motives of the patentee. In this case, he inferred that the motive for de-designating the UK (whilst maintaining the patents and applications in other countries) was to shield the portfolio from the risk of an adverse decision of the English Patents Court. This was notwithstanding that the UK market was significantly smaller in value than the rest of the European market. Birss J emphasised that Roche's prosecution strategy was not unlawful, and that it was entitled to try to obtain a valid patent for one of the indications claims through its filing strategy, even if that caused uncertainty to third parties. However, this should not prevent the court from making an *Arrow* declaration in light of the shielding behaviour if the circumstances were in Pfizer's favour.

UK rights and foreign spin-off value in the assessment of useful purpose

Pfizer contended that the *FKB v AbbVie* case suggested the Court should grant an *Arrow* declaration even when no UK rights were in existence. In that case, AbbVie offered complicated undertakings to abandon future UK rights and yet the Court decided nevertheless to grant the relief sought. However, Birss J was satisfied that the Court in that case had established a useful purpose in the declarations based on the commercial uncertainty in the UK market, that would remain despite the undertakings offered, and that *Arrow* declarations would dispel uncertainty in the UK. The judge also noted that

although Carr J in the *FKB v AbbVie* case acknowledged the potential effect of the *Arrow* declaration on the rest of the European market he had expressly not taken into account the spin-off value of the judgment abroad in his assessment of useful purpose.

In the present case, it was contended that the supply chain for Pfizer's bevacizumab product would be impaired if Roche decided to enforce its pending patents in Belgium. Birss J, however, distinguished Roche's actions to abandon all existing and future UK patent rights in question and found them to leave no uncertainty as to the rights in the UK following expiry of the SPC, as opposed to AbbVie's unclear undertakings in the earlier case which did not provide certainty for third parties.

The Judge also conducted a detailed analysis of Belgian law, including expert evidence presented by the parties on Belgian law, and the potential effect of a UK judgment on Belgian court decisions. Although he acknowledged that a Belgian court would undoubtedly consider a reasoned UK judgment, it was unlikely for it to rely completely on a foreign court's reasoning and would thus proceed to analyse the facts itself. He did acknowledge that an *Arrow* declaration from the English Court, along with the reasoned judgment, would be taken into account and would play a significant role in resisting preliminary measures such as a preliminary injunction on the basis that it would rebut the presumption of validity of a Belgian patent in interim proceedings.

Overall, Birss J noted that if there had been any pending UK patent applications in any of the families then this would have been a plain case for an *Arrow* declaration and he would have gone on to examine the technical merits of the *Gillette* defences (i.e. lack of novelty/obviousness) in detail. However, the complete absence of UK rights meant in reality that the commercial value of the declaration was the utility it might have in helping Pfizer defend itself against actions brought by Roche in other countries. Unlike the *FKB v AbbVie* case, there was no outstanding uncertainty relating to UK rights. Although there was uncertainty to the supply chain, that was a result of uncertainty created by pending Belgian patent applications. Although the result of a Belgian action could have an impact in the UK, that had nothing to do with any UK legal right.

The judge was not persuaded that use of the *Arrow* declarations and judgment in foreign courts was enough basis on which to grant the declarations, and so he refused to grant the declarations sought. As a result, he did not examine the merits of the *Gillette* defence in any detail.

Ultimately, Birss J adopted a wide interpretation of the discretionary power of the Court, and Roche were only able to resist the grant of the *Arrow* declarations (and a fully reasoned judgment) on the technical issues by abandoning all present and future UK rights. The

judgment suggests that in many cases, anything short of this nuclear option by the patentee will result in a case proceeding to trial⁷ and potentially unfavourable findings (to the patentee) being made at trial. Even in this case, the judge made a series of unfavourable observations about the likely strength of Roche's patent portfolio in light of various decisions made during both prosecution and the course of the UK action. Parties should therefore take heed of the potential that a claim for an *Arrow* declaration for causing damage to a patentee even if the claim is ultimately dismissed.

¹ *Arrow Generics v Merck & Co* [2007] EWHC 1900 (Pat)

² Named after the case of *Gillette Safety Razor v Anglo-American Trading Co* (1913) 30 RPC 465

³ *Fujifilm Kyowa Kirin Biologics v AbbVie* [2017] EWCA Civ 1

⁴ See paragraph 98 of the judgment of Floyd LJ

⁵ *FSA v Rourke* [2002] CP Rep 14

⁶ *Fujifilm Kyowa Kirin Biologics v AbbVie* [2017] EWHC 395 (Pat)

⁷ In fact Roche had previously attempted (unsuccessfully) to have the action dismissed at an interim stage on the basis that the UK rights had been abandoned. However, the Court held that the exercise of a discretionary power required an analysis of the facts at trial and so did not dismiss the action on a summary basis

Takeda revokes Roche patent to glycosylation pattern extending to Entyvio



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Takeda's product Entyvio contains the monoclonal antibody vedolizumab and is used as a treatment for Crohn's disease and ulcerative colitis. In the treatment of these autoimmune diseases, in order to prevent depletion of the patient's white blood cells, it is preferable to block targeted T cells from entering the gut, rather than to cause death of those cells. Vedolizumab operates by binding to X4β7 integrin and prevents T cells expressing this integrin from migrating into the gut.

Roche's patent EP (UK) 2 007 809 ("the Patent") claimed a monoclonal human IgG1 or IgG3 antibody glycosylated at position Asn 297 characterised by the amount of fucose, N-glycolylneuraminic acid (NGNA) and N-terminal alpha 1,3 galactose (a-Gal) residues within the sugar chain. Antibodies with a high degree of fucosylation exhibit reduced antibody dependent cellular cytotoxicity (ADCC), an effector function which is triggered when an antibody binds to its target cell and ultimately results in cell death via lysis.

Roche alleged that Entyvio infringed the Patent and Takeda alleged that the Patent was invalid, on a large number of grounds. The case was heard by Birss J in the Patents Court, who gave a lengthy judgment dealing with a number of technical issues on antibody technology¹.

What did the claims mean?

There were two key areas of dispute between the parties on the meaning of the claims of the Patent: (i) how to establish the level of fucosylation required by the claim; and (ii) the meaning of the term "antibody" as used in the claim.

Fucosylation levels

The parties put forward several possible methods of calculating whether an antibody would meet the required 99% fucosylation level specified in the claims. The judge preferred a calculation (referred in the judgment as TRM) that involved taking into account all fucosylated glycans (for the numerator in the calculation) and all higher mannose species (for the denominator). Notwithstanding the expert evidence, which suggested that all the calculations proposed by the parties involved “crazy math”, the judge opted for what appeared to be the “least crazy” option. Adopting this calculation, vedolizumab satisfied the level of fucosylation required by the claims.

Antibody, as used in the Patent

In the specification, the Patent explained that an “antibody according to the invention contains at least a functionally active (FcR binding) Fc part of IgG1 or IgG3 type comprising glycosylated Asn 297.” Although the skilled person would be familiar with the term ‘antibody’ used in the claims, the judge found that in the Patent the word had a special meaning and included only antibodies having a functionally active (FcR binding) Fc region, with glycosylation at Asn 297.

The Fc region of vedolizumab contains a mutation referred to as the “LAGA mutation”. Takeda’s case was that the LAGA mutation had been engineered so as to disrupt Fc receptor binding (substantially reducing ADCC) and, accordingly, the Patent was not infringed. Although a small degree of binding may remain, and indeed this was shown to be the case by surface plasmon resonance (SPR) assay experiments conducted by Roche on vedolizumab, there was no evidence that a functional effect takes place as a result of the binding. Roche’s position was that its experiments showed some, albeit small, binding and vedolizumab therefore has an Fc region which is functionally active, falling within the claim. According to Roche, as vedolizumab exhibits no ADCC, the high level of fucosylation in the antibody contributed to the absence of ADCC given that some Fc region binding was present.

The judge found that the LAGA mutation was not regarded as something that would necessarily eliminate functions such as ADCC altogether. Roche’s experiments showed some binding to the receptor by vedolizumab. Although it was “a close call”, the judge held that on the evidence it was more likely than not that the level of fucosylation made some contribution to the absence of ADCC. Accordingly, vedolizumab would infringe the Patent, if valid.

Validity

An important preliminary finding made by the judge was that, at the priority date in 2006, the skilled team had within its common general knowledge the know-how to make an antibody to a given target antigen. While this required a lot of work it was not an undue burden. This was determinative in his assessment of whether certain prior art documents not only disclosed the invention, but also enabled the skilled person to work the invention without undue burden.

Novelty

Takeda alleged that the Patent lacked novelty over three articles (Bihoreau, Shinkawa and Ferrara) and the prior use of a Novartis antibody called basilixumab (Simulect). Each of the pieces of prior art disclosed an antibody with the claimed levels of fucosylation. In the case of Simulect, the skilled person would have been able to analyse the glycosylation pattern of the antibody.

Roche argued that the prior art citations were not enabling, on the basis that the skilled person could not make the respective antibodies they disclosed. The judge found that this was not the correct test, however, and it was sufficient that the skilled person can produce a variation of the disclosure falling within the claim. Taking Bihoreau as an example, while the skilled person might not have been able to make the exact particular antibody disclosed in a prior art document that had the required level of fucosylation (in the absence of amino acid sequences) that does not mean the disclosure was not enabled. This piece of prior art reported the cell line used, even if not the expression vector or particular clones for producing the particular antibody disclosed. Whilst accepting that the skilled team would not be able to make the very antibody disclosed, the judge held that there was an enabling disclosure because the skilled team could make their own version of an antibody to the same target as disclosed in the prior document. The skilled team would express their own antibody sequence in the CHO-DG44 cells as described in the prior art document, they would make a number of subclones and screen for the level of fucose and galactose content. This would be a great deal of work, but the skilled person could make their own version of the antibody having the same fucose and galactose content as reported in the prior art document for the prior-disclosed antibody. The levels of NGNA and a-Gal were not disclosed, but the test for novelty was nonetheless satisfied, since the antibody produced by the skilled person would inevitably fall within the levels of NGNA and a-Gal set out in the claims. This was a result of the expression in CHO-DG44 cells.

Inventive step

The case highlights the difference between the tests for novelty and obviousness. Takeda did not run a conventional obviousness attack over Bihoreau, with the judge accepting Roche's evidence, in the absence of evidence or submissions to the contrary from Takeda, that if the skilled team followed up the Bihoreau disclosure they would not have set about making antibodies with very high fucosylation levels.

The focus of the Bihoreau document was on fucose to galactose ratios and thus it was not obvious to produce an antibody with the very high fucose levels of the claims, even if there was one antibody that did have the claimed levels of fucose (referred to above under novelty).

Instead, Takeda argued that the Patent offered no technical contribution to the art and thus lacked inventive step on this basis. Takeda relied on the general principle, arising from the EPO Technical Boards of Appeal case *Agrevo/Triazoles* T 939/92, that the patent monopoly as defined by the claims should correspond to the technical contribution to the art. Roche sought to advance three technical contributions centred around the high level of fucosylation, how it can be achieved in practice and its therapeutic utility. The judge adopted five questions in his assessment – Is the alleged technical contribution disclosed in the patent? Is it plausible? Is it true? Is it a technical advance? Does it support claims of the breadth they are?

Each of Roche's alleged technical advances failed on the basis that they either did not represent a technical advance, or were not rendered plausible by the Patent. Roche argued that a technical contribution made by the Patent was that 99% fucosylation of an antibody reduces ADCC to background. However, it was not clear that this was true at concentrations of antibody higher than the specific concentrations of antibody for which data were presented in the Patent and accordingly this was not plausible. In relation to the level of fucosylation, this feature alone could not support an inventive step since the contribution of the alleged technical advance was limited to antibodies expressed in CHO cells, and fucosylation was well known at the priority date to depend on cell type. Finally the idea of using increased fucose levels for a therapeutically useful purpose (the third alleged technical contribution) was not a technical advance over what was known as the idea that reducing ADCC was therapeutically useful for certain antibodies was part of the CGK and so too was the idea that increasing fucose would reduce ADCC. As a result the judge held that Patent invalid under the head of obviousness for lack of technical contribution.

Insufficiency

Takeda's case that the Patent was insufficient was based on allegations of ambiguity, breadth of claim (linked to the lack of technical contribution) and classic insufficiency. The judge found that the claims were truly ambiguous and invalid. This was grounded in the expert evidence that the skilled team, when given the patent, would think they could analyse peptides using two different analytical methods (two different types of liquid chromatography-mass spectrometry) and, depending on which one they used, they would get a different result on the characterisation of the antibody glycosylation pattern.

It will be interesting to see whether the judge's approach to assessing novelty and the technical contribution will be adopted more widely.

¹ Click for the full judgment: [Takeda UK v F. Hoffman-La Roche, \[2019\] EWHC 1911 \(Pat\)](#)

Jurisdiction challenge succeeds on appeal as contractual exclusive jurisdiction clause has priority



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In its recent decision in *Ablynx v VHsquared*¹ regarding the interpretation of EU Regulation 1215/2012 (or Brussels I Recast, as it is generally known), the Court of Appeal has clarified the correct approach to be taken when determining which court should decide who has jurisdiction in circumstances where parallel actions are ongoing. Whilst much will turn on the specific facts of each case, the judgment also serves to highlight the continuing relevance of exclusive jurisdiction clauses in patent licence agreements.

Background

The dispute related to three European patents (each of which had a UK designation) concerning immunoglobulins derived from camelid (being an animal family including camels and llamas) antibodies (the “Patents”). The Patents had been subject to various licences and a dispute arose between two of the licensees, Ablynx NV (“Ablynx”) and VHsquared Limited (“VHsquared”).

The Patents were owned by the Belgian university, Vrije Universiteit Brussel (“VUB”). In 1997, VUB granted a worldwide licence under the Patents to Unilever NH (the “Unilever Licence”) for certain applications of the licensed inventions. In particular, the Unilever Licence comprised an exclusive licence to exploit the Patents in certain named sectors including “packed food products” and “cosmetics with a non-medical orientation” and a non-exclusive licence to exploit the Patents in a few further named fields (together, the “Reserved Sector”).

Crucially, the Unilever Licence included a Belgian governing law clause and a choice of jurisdiction clause conferring exclusive jurisdiction on the Belgian court. In 2010, Unilever granted VHsquared a non-exclusive sub-licence to exploit the inventions in the Reserved Sector (the “VHsquared Licence”).

Meanwhile, in 1998, VUB granted an exclusive worldwide licence under the Patents to an institute (known as VIB) which allowed for the exploitation of the inventions in all fields except the Reserved Sector. In 2001, VIB granted an exclusive sub-licence to Ablynx (the “Ablynx Licence”) which necessarily also excluded the Reserved Sector. Accordingly, by 2011, VHsquared had a non-exclusive licence to exploit the inventions in the Reserved Sector (being, broadly speaking, non-medicinal fields) and Ablynx had an exclusive licence to exploit the inventions in all fields except the Reserved Sector.

In proceedings before the Courts of England & Wales (the “UK Court”), Ablynx alleged that VHsquared had infringed the UK designations of the Patents by carrying out certain activities which fell within the scope of Ablynx’ licence including, inter alia, conducting research into the use of camelid derived proteins for the treatment of gastrointestinal pathogens. In response, VHsquared contested the jurisdiction of the UK Court to hear the claim and subsequently issued proceedings in Belgium regarding Ablynx’ standing to sue in respect of VHsquared’s activities and whether those activities fell within the scope of the Unilever Licence. Although VHsquared did not enter an appearance before the UK Court, except to contest jurisdiction, it indicated that it intended to raise a number of defences to the action including limitation, experimental use, acting within the scope of the licence and invalidity of the Patents. Although the UK Court was the court first seised, proceedings were also ongoing in Belgium and a question therefore arose regarding which court had jurisdiction over the substantive dispute.

Brussels I Recast

Whilst it is not necessary to delve into Brussels I Recast in any great detail in this short report, a few particular provisions should be borne in mind. First, Article 24(4) provides that, in proceedings concerned with the validity of a patent, the courts of the Member State in which the patent is registered shall have exclusive jurisdiction. Second, Article 25(1) allows parties to grant jurisdiction to the courts of a selected Member State, including by way of exclusive jurisdiction, albeit that Article 25(4) provides that agreements conferring jurisdiction shall have no legal force if the courts whose jurisdiction they purport to exclude have exclusive jurisdiction by virtue of Article 24. Third, Article 31(2) provides that, where a court of a Member State on which an agreement as referred to in Article 25 confers exclusive jurisdiction is seised, any court of another Member State shall stay proceedings until such time as the court seised according to the exclusive jurisdiction provision declares it has no jurisdiction.

The first instance decision

At first instance, His Honour Judge Hacon found the UK Court had exclusive jurisdiction and refused to stay the proceedings in the UK. Applying Article 25(4), the judge found that the exclusive jurisdiction clause in the Unilever Licence had no legal force in circumstances where it purported to exclude the UK Court's jurisdiction under Article 24(4) as the action was likely to be concerned (even if not exclusively) with the validity of the UK designation of European patents. In reaching this conclusion, HHJ Hacon first considered whether Article 24(4) was engaged (he found that it was based on the indication from VHSquared as to its intended defences), next whether Article 25(4) was engaged (again, he found that it was), and, finally, whether Article 31(2) was engaged (he found that it was not).

The Appeal

The main thrust of VHSquared's appeal was that, in accordance Article 31(2), it was for the Belgian court (rather than the UK Court) to decide which court had jurisdiction. In other words, in addition to the question of which court had jurisdiction over the substantive dispute, there was a preliminary question regarding which court should decide who had jurisdiction over the substantive dispute.

Having considered the philosophy underlying various articles of Brussels I Recast, the Court of Appeal agreed with VHSquared's characterisation of Articles 24(4) and 25(4) as "substantive rules of jurisdiction" and Article 31(2) as a "procedural rule" about which court should decide the question of jurisdiction where parallel actions are ongoing.

Contrary to the approach adopted by Hacon HHJ, the Court of Appeal first considered whether Article 31(2) was engaged. In answering this question, the Court of Appeal agreed that the test to be applied by the court first seised (here, the UK Court) was whether there was a *prima facie* case that there is an exclusive jurisdiction clause in favour of the court in another Member State. In addition, it was necessary to consider whether there was a *prima facie* case that Ablynx was bound by the exclusive jurisdiction clause and that the proceedings between Ablynx and VHSquared fell within the scope of the jurisdiction clause. Whilst it was ultimately for the Belgian court (being the court designated in the exclusive jurisdiction clause) to determine the question definitively, the Court of Appeal held that on the information before it there was a *prima facie* case that Article 31(2) applied.

Next, the Court of Appeal considered whether Article 25(4) was engaged. As before, this question was to be decided on a *prima facie* basis. In applying Article 25(4), the Court of Appeal considered the extent of the UK Court's exclusive jurisdiction under Article 24(4). Following guidance from the CJEU in *Berliner Verkehrsbetriebe v JP Morgan Chase Bank*² and the UK Supreme Court in *Koza v Akçil*³ in which the question of exclusive jurisdiction in Article 24 depends on whether the "principal subject matter" of the action concerns the reserved subject matter, the Court held that a number of defences intended to be raised did not involve attacking the validity of the Patents nor were they inextricably linked with such an attack. On the basis that the exclusive jurisdiction provisions of Article 24 should be narrowly interpreted and in circumstances where the dispute between Ablynx and VHSquared was an action raising multiple issues including the scope of a licence, the Court of Appeal considered that VHSquared had established a *prima facie* case that Article 24(4) did not pull all the issues into the exclusive jurisdiction of the UK Court. Similarly, the Court of Appeal found it to be arguable that Article 25(4) did not invalidate the exclusive choice of court clause. As in the context of Article 31(2), it was for the Belgian Court to determine these questions definitively.

Having allowed VHSquared's appeal, the whole of the UK proceedings were stayed pending a decision from the Belgian Court on whether it has jurisdiction and, if it does, on the scope of the VHSquared Licence.

¹ *Ablynx NV & Anr v VHSquared Limited* [2019] EWCA Civ 2192

² Case C-144/10 *Berliner Verkehrsbetriebe (BVG) v JP Morgan Chase Bank NA* EU:C:2011:300

³ *Koza v Akçil* [2019] UKSC 40

The Regulation of Software Medical Devices



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Background

Pharmaceutical products and software medical devices are converging at an increasing rate – reflecting a trend towards personalised medicines. In some cases, this is relatively uncontroversial, such as the use of an App to track treatment regimens. In others, it is more complex, such as the use of sophisticated technology to determine and target medicinal treatments for individual patients. In any case, it is evident that traditional pharmaceutical companies need to be aware of developments in the regulation of software medical devices.

Against that background, the EU Medical Devices Regulation (2017/745) (EU MDR) was intended to come into full effect on 26 May 2020^{1,2}, repealing and replacing the Medical Devices Directive³ (MDD).

Software under the EU MDR

The EU MDR takes a far more direct (and strict) approach to classifying software than the MDD. In part, this reflects the increased sophistication and prevalence of software. Under the EU MDR, nearly all software medical devices will be up-classified from class I (the lowest risk class) to class IIa or above. This will require the involvement of a Notified Body for the first time. The source of this dramatic up-classification is Rule 11, Annex VIII of the EU MDR.

The phrasing of Rule 11 is very wide. First, it classifies all software medical devices which are “*intended to provide information which is used to take decisions with diagnosis or therapeutic purposes*” as at least class IIa. Most software medical devices on the market are clearly intended to provide information of this kind. For example, even software that operates as a thermometer would be captured, as the information generated is used to take diagnostic or therapeutic decisions.

In many cases, these devices will be further up-classified to the highest risk class: class III. Rule 11 of the EU MDR provides that if the decisions taken “*may*” cause death or an irreversible deterioration of a person’s state of health, the relevant device is class III. The term “*may*” in this context is very broad – to escape it, one would presumably have to prove that these events could not occur. In the case of medical devices, it is very difficult to identify a decision made on the basis of information from a device which could *never* cause death or permanent deterioration. To return to the example above, even a decision made on the basis of information provided by a simple software-based thermometer could cause death, if the decision was to delay treatment.

As such, there has been concern in the medical devices industry that many (or even all) software medical devices could be classified as class III. Compounding that concern, there was no formal guidance available until very recently on how Rule 11 would be applied.

The MDCG Guidance

On 11 October 2019, the Medical Device Coordination Group (MDCG) released *Guidance on Qualification and Classification of Software*⁴ (Guidance). The Guidance appears to attempt to soften the effect of Rule 11. It does so by reference to the position adopted by the International Medical Device Regulators Forum⁵ (IMDRF). The IMDRF approach is based on the significance of the information the software provides to an eventual healthcare decision, in combination with the condition of the patient.

The Guidance suggests that in classifying a device, a manufacturer should assess the influence of information provided by the device. For example, will it be determinative in a patient’s treatment, or just one factor. It also allows for assessments to be made as to the seriousness of the patient’s condition. For example, is the software influencing the treatment of cancer or a cold? These distinctions would allow manufacturers and Notified Bodies to be more pragmatic in classifying software medical devices than a strict reading of Rule 11 alone, although the Guidance is not legally binding.

The Corrigendum

Compounding the problems raised by an initial lack of guidance, manufacturers have faced a severe limitation on Notified Body capacity. All Notified Bodies are required to re-certify under the EU MDR. At the time of writing, however, only seven Notified Bodies have achieved this – by contrast, there were nearly 60 Notified Bodies actively assessing against the MDD. This combination of more manufacturers needing Notified Bodies with fewer Notified Bodies being available has given rise to an ‘approval bottleneck’, which could lead to serious shortages of devices if it continues⁶.

In response, the Environment, Public Health and Food Safety Committee of the European Parliament recently approved a corrigendum⁷ to the EU MDR (**Corrigendum**), which provides a four-year 'grace period' for class I medical devices which are up-classified by the EU MDR. The Corrigendum, which was approved on 17 December 2019⁸, provides devices that had a declaration of conformity issued under the MDD prior to 26 May 2020, and that require a Notified Body for the first time (i.e. most software medical devices), to continue to be placed on the market until 26 May 2024. This will afford more time for affected software medical device manufacturers to obtain a Notified Body and achieve compliance with EU MDR requirements.

Summary

While the regulatory requirements for software medical devices are increasing, the Guidance and the Corrigendum provide for more flexibility and time than originally anticipated. In light of this, perhaps the forecast for software medical devices is not as stormy as it was six months ago. Indeed, in September, Biotronik's '*Renamic*' programming software, which is a device that allows clinicians to program implanted cardiac devices, received certification under the EU MDR from German Notified Body TÜV SÜD. As far as we are aware, this is the first software medical device approved under the EU MDR. Hopefully, it heralds many more.

¹ This article does not address 'Brexit' but for completeness, we note that the EU MDR will be incorporated into UK law (with necessary amendments) in the event of a no-deal 'Brexit', including at the end of the transitional period under the envisaged Withdrawal Agreement between the UK and EU (dated 21 October 2019)

² Since this article was written it has been confirmed that implementation has been delayed by 12 months due to the COVID-19 pandemic

³ Council Directive 93/42/EEC

⁴ https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en

⁵ <http://www.imdrf.org/>

⁶ <https://www.medtecheurope.org/news-and-events/news/medical-device-industry-position-on-the-implementation-of-the-new-medical-device-regulation/>

⁷ <https://data.consilium.europa.eu/doc/document/ST-13081-2019-INIT/en/pdf>

⁸ <https://www.europarl.europa.eu/plenary/en/infos-details.html?id=17721&type=Flash>

The Court of Justice confirms the EMA's approach to transparency



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The evolution of the EMA's approach towards transparency has probably been one of the biggest policy changes within the institution in the last decade. Conscious of what was at stake, the industry soon embraced the changing times and evolved towards improved openness and data sharing. The breeding ground of the evolution, which can be classified as a paradigm shift in the EMA, was a more active involvement of patients in their care, the increasing role of patient associations, the growth of research in academia, a general societal trend towards transparency, together with the enactment of Regulation (EC) 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (the "Transparency Regulation").

The Court of Justice has recently had the chance to rule on the application of the Transparency Regulation in two cases which raised almost identical issues concerning the right of third parties to access documents held by the EMA. In Appeals C-175/18 P¹ and C-178/18 P² the Court of Justice upheld the decisions of the General Court and, in turn, those of the EMA to release documents which were submitted as part of marketing authorisation applications, despite the diverging Opinion of Advocate General Hogan.

The decisions

Both PTC Therapeutics International Ltd ("PTC") and MSD Animal Health Innovation GmbH and Intervet International BV (together "Merck") argued, before the EMA and the Court of Justice of the European Union, that documents submitted as part of their respective marketing authorisation applications (a case study report in the case of PTC and a toxicology report in the case of

Merck) should be presumed to be confidential in their entirety and, for that reason, should not be released in response to a third party application to access said documents under the Transparency Regulation.

In its two judgments of 22 January 2020 the Court of Justice clarified that:

- The principle of the widest possible public access to documents has some exceptions (article 4 of the Transparency Regulation). In this regard, the right to access is subject to certain limits based on reasons of public or private interest such as the undermining of the protection of commercial interests of the proprietor of the document. As an exception, the above mentioned provision should be interpreted strictly.
- For a proprietor to benefit from the abovementioned exception, it must explain how access to that document could “*specifically and actually undermine the interest protected by that exception*” and “*the risk of the interest being undermined must be reasonably foreseeable and must not be purely hypothetical*”. The Court of Justice agreed with the Advocate General that the test set by the General Court that any disclosure had to “seriously” undermine the protection of the proprietor’s commercial interest for the purposes of bringing the exception into play is too elevated a standard. The Court of Justice concluded that “*any undermining of the interests concerned is capable of justifying the application, as the case may be, of one of the exceptions*” in article 4 of the Transparency Regulation.
- Contrary to the Opinion of the Advocate General, the Court of Justice has ruled against a general presumption of confidentiality. Indeed, the recourse to a general presumption of confidentiality is merely an option for the EU institution or agency concerned and the latter always retains the possibility of carrying out a specific and individual examination of the documents in question to determine whether they are protected, in whole or in part, by one or more of the exceptions of article 4 of the Transparency Regulation, including the one related to commercially confidential information.

Conclusion and implications

Unsurprisingly the CJEU broadly supports the EMA’s approach towards the Transparency Regulation. There is one useful takeaway from the decisions for proprietors of documents held by the EMA which are subject to a third party request to access them: when presented with the opportunity to express their views on the possible confidentiality of certain information contained in the document, proprietors should not provide a mere unsubstantiated claim to a general risk of misuse. On the contrary, they must precisely and specifically identify the part or parts of the document which, if

disclosed, would harm their commercial interests. Only if proprietors explain how access to a document could specifically and actually undermine their interest and are able to convey that the risk of undermining said interests is reasonably foreseeable (as opposed to purely hypothetical) will they have chances of succeeding with the redaction of those parts of the document which are truly commercially confidential.

Notwithstanding the above, these cases will be of little value, other than historical, once Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (“Clinical Trials Regulation”) becomes applicable³. Indeed, the culmination of the shift towards transparency is enshrined in the legal obligation of applicants of marketing authorisation to make publicly available, via the EU database to be set up by the EMA, the clinical study report within 30 days after the day the marketing authorisation is granted, the procedure for granting the marketing authorisation is completed, or the application is withdrawn. The application of the Clinical Trials Regulation will put an end to most of the litigation around the disclosure of clinical study reports, as the legislature considered that in general the data included in said report should not be considered commercially confidential once a marketing authorisation has been granted.

¹ Click for the full judgment [here](#)

² Click for the full judgment [here](#)

³ According to the information provided by the EMA in March 2020, the Clinical Trials Regulation will not become applicable before 2021

Clarity sought on plant patentability



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2019 saw a further twist in the long-running saga on the provisions in the Biotech Directive (Directive 98/44/EC) and European Patent Convention (EPC) regarding patentability of the products of “essentially biological processes”. By way of reminder, Article 4 of the Biotech Directive states that “*essentially biological processes for the production of plants or animals*” shall not be patentable and the exclusion thus applies in all EU signatory states to the EPC. Following introduction of the Biotech Directive, the EPC was modified to include the same exception to patentability in Article 53(b) (brought in with the changes to EPC 2000). Both provisions are silent as to the plant (or animal) products of those processes. Notwithstanding the virtually identical wording, and the fact that the EPC was specifically modified so as to be aligned with the changes introduced in the majority of its signatory states as a result of the Biotech Directive, there has been some divergence as to the correct interpretation of the provision.

A short history lesson is required to understand the current situation. In 2015, the Enlarged Board of Appeal (EBA) of the European Patent Office (EPO) was required to consider the scope of the exception in the Tomato II and Broccoli II cases (G2/12 and G2/13). The EBA concluded that a narrow interpretation of Article 53(b) EPC was appropriate and as a result plants and animals derived from essentially biological processes were in principle patentable, even if they were inevitably derived from such processes.

Nevertheless, the European Parliament asked the EU Commission to consider various issues relating to the Biotech Directive, including the exclusion to patentability in question. The Commission reviewed the context and provisions of the Biotech Directive and published a notice on 3 November 2016¹ concluding that the intention of the EU legislators when adopting the Biotech Directive was to exclude such products from patentability.

In response to the Commission’s Notice, which diverged from the conclusions of the EBA in G 2/12 and G 2/13, the EPO published its own notice from the EPC Administrative Council clarifying that plants and animals exclusively obtained by means of an essentially biological process will no longer be patentable given the need to safeguard uniformity in harmonised European patent law. The Administrative Council also amended Rules 27 and 28 of the Implementing Regulations to the EPC, which came into force on 1 July 2017 and which applied to all (as then) pending and future patent applications. Rule 28(2) now reads: “*Under Article 53(b), European patents shall not be granted in respect of plants or animals exclusively obtained by means of an essentially biological process*”².

This appeared to have laid the matter to rest. However, in a subsequent case³ one of the EPO Technical Boards of Appeal (TBA) held that modified Rule 28(2) was void because it contradicted the interpretation of Article 53(b) EPC in 2015 by the EBA in the Broccoli/Tomato II cases. The TBA was also of the view that the EBA had already decided on the question and therefore a further reference to the EBA was not required.

This led to a referral in March 2019 by the President of the EPO to the EBA, purportedly under Article 112(1)(b) EPC, which allows the EPO President to refer a point of law to the EBA where two Boards of Appeal have given different decisions on that question.

The President has referred two questions to the EBA, as follows:

Question 1 – “*Having regard to Article 164(2) EPC, can the meaning and scope of Article 53 EPC be clarified in the Implementing Regulations to the EPC without this clarification being a priori limited by the interpretation of said Article given in an earlier decision of the Boards of Appeal or the Enlarged Board of Appeal?*”

Question 2 – “*If the answer to question 1 is yes, is the exclusion from patentability of plants and animals exclusively obtained by means of an essentially biological process pursuant to Rule 28(2) EPC in conformity with Article 53(b) EPC which neither explicitly excludes nor explicitly allows said subject-matter?*”

There is some uncertainty as to whether the EPO President’s referral is admissible, given that previous decisions of the Boards of Appeal appear to be aligned. On this, and in relation to the first question, the President has sought to rely on previous TBA decisions which suggest that the Administrative Council can issue Rules on interpretation of the EPC that are contrary to an earlier decision of a Board of Appeal (albeit that the previous decisions in the earlier cases were not those of the EBA). The referral by the President has attracted widespread comment, as well as over 40 amicus curiae from interested parties, including a number of Governments from member states to both the EU and EPC as well as

the European Commission itself. At present, although the referral has been given a case number (G 3/19), no decision has been made on admissibility or the merits of the questions themselves. We await to see what 2020 brings by way of developments in this area. In the meantime, whilst the referral remains pending, examination and opposition proceedings at the EPO relating to products produced by essentially biological processes have been stayed⁴.

¹ Click for the full judgment: [Notice 2016/C 411/03](#)

² Click for the full judgment: [OJ EPO 2017, A56](#)

³ T 1063/18 (Pepper)

⁴ Click for the full judgment: [OJ EPO 2019, A34](#)

“Pay-for-delay” settlement agreements in biotech: a European perspective on the US Humira litigation



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In recent years, “pay-for-delay” arrangements in the pharmaceutical sector have come under intense scrutiny from the European Commission and national competition authorities. The focus of the authorities thus far has largely been on traditional small-molecule pharmaceutical products. However, recent antitrust litigation in the USA relating to Humira (adalimumab) suggests that patent settlement agreements relating to biotech products may also be alleged to present competition law issues. This case is also the first to consider the whether allowing “early entry” in EU markets counts as a quid pro quo for staying off the market in the USA and whether, if so, that is an antitrust concern. It is therefore of interest not only to US antitrust lawyers, but also to EU competition law practitioners, as well as to the wider biotech industry.

In patent settlement agreements involving a ‘pay-for-delay’ element, the originator company makes a payment or provides some other benefit to the generic company. In return for this payment, the generic promises to respect the patent and stay off the market for a period of time. To date, these agreements have generally been viewed by competition authorities and courts as anti-competitive (see, for example, the General Court’s judgments in *Lundbeck*¹ and *Servier*², and the CMA’s decision in the UK *Paroxetine* case³), as they remove the possibility of early entry by cheaper generic products. Such ‘reverse payments’ are considered to act as an inducement to the generic to accept what would otherwise be an unacceptable fetter on its market access. The recent Court of Justice Paroxetine judgment (a response to a preliminary reference by the UK Competition Appeal Tribunal) confirmed that entering into agreements of this kind may, in certain

circumstances, amount to an infringement of competition law by object⁴. Although the European courts have yet to consider how pay-for-delay agreements between potential biotech competitors would be assessed, it should be assumed that the same basic principles would apply.

Background to the litigation

In March 2019, a private antitrust suit was filed in the Illinois Northern District Court against AbbVie and biosimilar companies including Amgen, Pfizer and Mylan by UFCW, a healthcare benefits provider, on behalf of indirect US purchasers of Humira (adalimumab). Humira is a monoclonal antibody treatment developed and marketed by AbbVie, which is used to treat chronic immune-related diseases including rheumatoid arthritis, psoriasis and Crohn's disease. The primary patent for Humira expired in the US in December 2016. However, AbbVie holds over 100 other patents for Humira, with expiry dates up to at least 2034.

The main allegations against AbbVie and the settling biosimilar companies are that:

1. AbbVie has created and employed an exclusionary "patent thicket" of over 100 patents in order to provide long-term insulation to Humira from any biosimilar competition;
2. AbbVie has used its patents to enter into illegal market-division agreements with the co-defendants in a bid to delay biosimilar entry in the US. (Even though the settlement agreements allow US entry at an agreed date which is before the patent expiry in 2034, this is still alleged to be a pay-for-delay arrangement.) Meanwhile, AbbVie permitted biosimilars of Humira to launch as early as October 2018 in the EU market (following SPC expiry in the EU);
3. AbbVie's prolonged monopoly has resulted in US patients paying artificially higher prices compared to European patients, who benefitted from competition; and;
4. The lower price for Humira in Europe was effectively "subsidised" by the much higher price in the US where AbbVie unlawfully maintained its monopoly.

Pay-for-delay in the EU and US

From an EU perspective, pay-for-delay agreements have been held to be "by object" restrictions of competition under Article 101 TFEU (*Lundbeck Paroxetine*). The Humira plaintiff takes a similar view, asserting that "*The unlawful market division arrangements are per se violations of the Sherman Act*"⁵. However, the US courts have previously taken a more nuanced view of pay-for-delay settlements between originator and generics manufacturers. In *FTC v Actavis*⁶, the US Supreme Court stated that the pay-for-delay cases should be analysed using a "rule of reason" approach – albeit at the "quick

look" standard – rather than the stricter "*per se*" rule. To date, however, the US Supreme Court has not yet had cause to look at non-financial incentives within patent settlement agreements of the type alleged in the Humira case.

The strong US policy in favour of protecting innovation (including the filing of patents) also suggests that establishing a patent thicket has anticompetitive effect is likely to be difficult. Nor is it clear that the US Court will agree that the biosimilar manufacturers – of which a number were yet to receive FDA approval – would have had a realistic prospect of entering the market in the absence of the settlement agreements.

In previous EU pay-for-delay cases, the courts have considered whether the existence of patent rights could create an insurmountable barrier to entry. They have generally concluded that the existence of process (or other secondary) patents was not enough to preclude potential competition in the market: once the primary patent over the active ingredient has expired, the market "is in principle open"⁷.

There is also no clear position on whether the EU authorities would be willing to tackle patent thickets. The Commission did refer in its *Servier* decision to the existence of a portfolio of process patents which made it "more difficult, costly and lengthy for potential entrants to identify the scope of Servier's valid patent protection and thus develop a viable product for potential entry"⁸. However, this statement was not formally presented as an allegation of abuse, and in any event, the General Court overturned the Commission's abuse of dominance finding in this case. One earlier case was closed following a settlement between the parties involved in the underlying patent dispute⁹.

Generics vs biosimilars

Whether or not the findings in previous pay-for-delay cases also apply to biotech companies remains to be seen; although the markets are similar, biosimilars differ from small-molecule generics in several ways. For example, the higher costs associated with the development of a biosimilar compared with a generic drug result in an reduced asymmetry of risk between the originator company and the biosimilar company upon the launch of the biosimilar. Moreover, doctors may be more hesitant to switch patients to biosimilars than they are to switch patients to generics due to a lack of guidance on interchangeability between originator biologics and biosimilars, and so a less extensive and immediate loss of sales of the originator product may be seen upon the launch of a biosimilar compared to the launch of a generic.

There may therefore be less of an incentive for originator companies to "pay-off" their biosimilar competitors in exchange for the promise of delayed entry onto the market. Taking into account the economic and scientific

context, it may therefore be the case that the relationship between biologics and biosimilars cannot be viewed as equivalent to that of small molecule originators and generic manufacturers.

Allowing early entry in the EU - a “value transfer”?

The allegations in the Humira case do not fit within the framework of a pure ‘pay-for-delay’ agreement, as there is no allegation of a monetary payment by Abbvie to the settling biosimilar manufacturers. Rather, it is alleged that those manufacturers benefited through being permitted to launch their products in Europe while remaining off the US market.

There are a number of reasons why a settlement agreement following litigation in different parts of the world may result in the parties agreeing a different approach for different territories. The scope of patent protection will not be identical in different regions, and the patentee may consider it has better prospects of success in some markets than others. From a more commercial point of view, it is also inevitable that some markets are worth more than others, and may be worth an investment in defending which it would not be worth making in a country with a smaller patient population. It may not make commercial sense to pursue market withdrawal from markets where at risk entry has taken place. It is uncontroversial that different patent protection may be put in place in different countries; it follows that litigation strategy, including decisions to settle, are likely to be similarly country-specific. It seems unlikely that competition rules would oblige a party to settle everywhere or nowhere.

However, that is not to say that a situation of this kind could never cause competition problems. The EU has looked at the question of settlements which result in a commitment to stay off some markets while allowing entry in others in the *Servier – Krka* case. In that case, Krka (the generic manufacturer) was involved in litigation with Servier in the UK, and (following a decision by the Opposition Division of the EPO to maintain the patent) agreed to settle that litigation on terms that it would stay off the UK market. Meanwhile, it had already entered certain Eastern European markets, and signed a licence agreement with Servier to formalise its market access. The Commission Decision treated the licence agreement as an inducement to Krka to agree to the UK settlement. However, the General Court rejected this analysis and held that as the licence agreement involved royalty payments at a fair market value, it followed that there was no inducement.

Conclusion

The course that this case takes will be important for all pharmaceutical companies envisaging global settlements, in particular where these lead to different market outcomes in different parts of the world. For now, biotech and other pharma firms should exercise caution when entering into patent settlement agreements that contain terms allowing entry at different times in different geographical markets.

¹ Cases T-472/13 etc. *Lundbeck v Commission* EU:T:2016:454

² Case T-691/14 *Servier v Commission* EU:T:2018:922

³ CMA decision of 12 February 2016, *Paroxetine – Case CE-9531/11*

⁴ Case C-307/18, *Generics (UK) Limited and Others v Competition and Markets Authority*. For more information on this judgment, see the recent article by Pat Treacy and Olivia Henry for Bristows’ life sciences blog, *On the Pulse*, at <https://www.bristows.com/news/competition-between-generics-and-originators-whats-the-relevance-of-a-patent-2/>

⁵ *UFCW Local 1500 Welfare Fund v AbbVie and ors* (class action complaint filed 18 March 2019), paragraph 127

⁶ *Federal Trade Commission v Actavis, Inc. et al.*, 570 U.S. __ (2013)

⁷ Commission Decision C(2013) 3803 final - *Lundbeck*, paragraph 68

⁸ Commission Decision C(2014) 4955 final – *Perindopril (Servier)*, paragraph 2770

⁹ https://ec.europa.eu/commission/presscorner/detail/en/IP_11_842

The CMA's Director Disqualification Power – a power now being put to use



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The UK Competition and Markets Authority (the “CMA”) has had the power to disqualify directors of companies that have been found to have infringed competition law since 2003. It is a power that, until the last couple of years, had scarcely been exercised – as at the end of 2018, only three directors had been disqualified through its use. However, in 2019, a further six directors were disqualified, and one case is now for the first time proceeding through the courts. With new CMA [guidance](#) on procedure issued in February 2019, the CMA itself stated that it has been “*ramping up how we use our disqualification powers and as a result, the risk of director disqualification to those who break the law has never been higher*”. This is therefore a power that the CMA is actively using, and is one that all companies operating on the UK market should be aware of. Although the power has not yet been publicly used in relation to cases in the pharmaceutical sector, it is a sector that remains a focus of the CMA’s enforcement activities; there is no reason to think that the CMA would treat the sector differently when it comes to director disqualification proceedings.

The power to disqualify directors on the basis of competition law infringements are contained in the Company Directors Disqualification Act 1986 (“CDDA”), which applies to England, Wales, and Scotland, and the Company Directors Disqualification (Northern Ireland) Order 2002.

Under the CDDA, a director or former director can be disqualified for up to 15 years, with any breach of that disqualification punishable by a fine and/or up to two years imprisonment. Disqualification can be effected in two ways: a voluntary but binding competition

disqualification undertaking may be given by a director (a CDU); or the CMA can apply to court for a competition disqualification order (a CDO). To date, all disqualifications have been by way of a CDU, although the CMA has applied for CDOs in two instances. One settled with a CDU before trial, and the other is due to be heard in 2020. The CMA has noted that the offering of CDUs have resulted in a shorter period of disqualification than would have been sought under a CDO procedure before the Court.

When deciding whether to apply for a CDO, the CMA will have regard to the seriousness of the infringement, its duration, the impact (or potential impact) on consumers, the company’s conduct during the course of the investigation, and whether the company had previously breached competition law. For a CDO to be made, two conditions must be satisfied:

- The company for which they are a director commits a breach of competition law; and
- The court considers that their conduct as a director makes them unfit to be concerned in the management of a company.

Whilst the first condition suggests (but does not require) that the CMA will have issued an infringement decision before it is satisfied, the CMA has recently changed its process, and now opens CDDA proceedings before the main investigation into any anti-competitive conduct has been concluded. Previously, the CMA stated it would only use its disqualification power after the conclusion of any appeal. This changed in June 2018, as the CMA now considers it to be more efficient for a CDO to be assessed at the same time as any infringement or penalty. While there may be efficiency gains (at least where the breach of competition law is clear-cut and highly likely to lead to an infringement finding), this also gives the CMA a procedural advantage of placing parties to investigations under increased pressure.

For the second condition, the Court must have regard to whether the director’s conduct contributed to the breach; if it did, it is immaterial whether they knew that the conduct was contrary to competition law. Alternatively, if a director’s conduct did not contribute to the breach, the legal test is whether the director had reasonable grounds to suspect that conduct constituted a breach and took no steps to prevent it, or whether s/he did not know but ought to have known that the conduct constituted a breach.

One of the key differences between insolvency based disqualifications, and competition disqualifications is that in the latter case, the company is likely to still be active. While this does not affect the disqualification process itself, it is likely to be important in any application for permission to act as a director (the court can give dispensation to directors to act in specific roles,

notwithstanding the disqualification). Indeed, in the first decision relating to permission to act following a competition law infringement handed down in December 2019, the High Court has given permission to act, in view of the strategic importance of the individuals to the companies in question and the potential for adverse impacts on those companies without the individuals being in place (In the Matter of Fourfront Group Ltd & Ors [2019] EWHC 3318 (Ch)).

While this ruling may somewhat temper the CMA's new enthusiasm for its power, directors should be looking to ensure that they protect themselves against breaches of competition law, by attending regular competition training, and maintaining a top down compliance culture; the key is not to become experts in competition law, but to demonstrate a commitment to diligence. National authorities of EU27 member states may also have chosen to implement a disqualification regime, and directors should familiarise themselves with the personal risks associated with each jurisdiction.

High Court dismisses GSK's claim that Sandoz's AirFluSal Forspiro inhaler passes off GSK's Seretide Accuhaler

Glaxo Wellcome (t/a Allen & Hanburys) v Sandoz & others¹



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In October 2019, Lord Justice Arnold gave judgment in a High Court claim between GSK and Sandoz relating to Sandoz's AirFluSal Forspiro inhaler². GSK alleged passing off, but its claims were dismissed in their entirety.

Background and marketing authorisation position

GSK sought to prevent the sale in the UK of the AirFluSal Forspiro, which is an inhaler for the treatment of COPD and asthma which contains the active ingredients combination of fluticasone and salmeterol. GSK alleged that the marketing of the AirFluSal Forspiro in its current colour, shape and packaging, amounted to passing off. Images of the two inhalers at issue are shown below.



GSK's Seretide Accuhaler



Sandoz's AirFluSal Forspiro

Seretide, which is available in the Accuhaler form shown above, as well as in a 'boot shaped' metered dose inhaler, has been one of the most commercially successful pharmaceutical products since its launch in 1999. Following the expiry of GSK's patents for the active ingredients combination within Seretide, the AirFluSal Forspiro and a number of other generics have been launched to compete with it.

Whilst Sandoz's AirFluSal Forspiro inhaler contains the same active ingredients as Seretide, those ingredients are delivered by a proprietary dry powder inhaler device. The AirFluSal Forspiro's marketing authorisation ("MA") was therefore obtained under the route provided by Article 10(3) of the Medicinal Products Directive (2001/83/EC), which is sometimes termed the 'hybrid' route. This is the appropriate route for a product such as a dry powder inhaler which dispenses a locally acting product, the action of which in the body may depend upon the pattern of distribution of the active ingredient as delivered into the patient's lungs. As a result of this route to market authorisation, the AirFluSal Forspiro's MA varies in scope to that obtained by for the Seretide Accuhaler. This distinction formed an important pillar of GSK's claims.

The alleged misrepresentations

GSK alleged the traditional form of passing off, i.e. a misrepresentation as to origin. However, as the trial approached, GSK's focus shifted to a more unusual argument, namely that the colour and appearance of the AirFluSal Forspiro amounted to a false representation that the AirFluSal Forspiro is "equivalent" to the Seretide Accuhaler. In this regard, GSK relied on the following differences between the competing products in support of this alleged misrepresentation:

1. The AirFluSal Forspiro has a narrower MA than the Seretide Accuhaler of an equivalent strength. In particular, the AirFluSal Forspiro was only licensed for COPD (not asthma) from its launch in November 2015 until February 2017 when the MA was varied. After that date, the MA was extended so as to also cover asthma, but only for adults with severe asthma.
2. The Seretide Accuhaler is available in three strengths, whereas the AirFluSal Forspiro is only available (in the UK) in the highest of these strengths. This allows Seretide Accuhaler patients to be titrated down to a lower strength Accuhaler when their symptoms are under control. The same patient who is using an AirFluSal Forspiro would have to switch inhalers at this point, for example to the mid-strength Seretide Accuhaler.
3. Patients require training when they first use the AirFluSal Forspiro, even if they have previously used a Seretide Accuhaler. That is because the two devices operate in very different ways.

The court's findings

The court heard extensive evidence from a number of healthcare professionals, including prescribing doctors, asthma specialists and dispensing pharmacists, who gave evidence regarding the manner in which respiratory products were licensed by the MHRA, prescribed to patients, and then dispensed. In addition, the court looked at the development of asthma treatments over time, and historical trends including with regard to the use of colours on inhalers. The judgment also considered the shift in recent years away from generic prescribing of asthma inhalers (particularly for dry powder inhalers) and also the reimbursement of inhalers such as the Seretide Accuhaler, which is a Category C medicine on the NHS's drugs Drug Tariff. All of this provided the context in which GSK's passing off claims were assessed.

In relation to GSK's origin confusion claim, the court found that there was no evidence that the purple colours used on GSK's Seretide inhalers had become distinctive of either GSK or Seretide. It was therefore unsurprising that there was also no evidence that patients (or indeed anyone else) had been misled as to the commercial origin of the AirFluSal Forspiro as a result of its appearance. The origin confusion claim was therefore dismissed.

In relation to GSK's equivalence claim, the court again found no evidence that the purple colour of Seretide was distinctive of the relevant characteristics of the Seretide Accuhaler, or that anyone was likely to be confused as to the characteristics of AirFluSal Forspiro due to its appearance, and in particular the use on that product of the colour purple. Instead, the healthcare professionals who gave evidence were all clear that they would not make any assumption about the marketing authorisations of inhalers based on their colour. The equivalence claim was therefore also dismissed.

What does the judgment mean for the wider industry

The judgment will be of particular interest to manufacturers of asthma and COPD inhalers, particularly generic inhalers and those authorised under the Article 10(3) 'hybrid' route. In particular, the Court looked in depth at the use of colours for asthma/COPD treatments, and in particular at how generic manufacturers have often used the same colour on their inhaler as the originator's product. Think, for example, of the various blue inhalers containing salbutamol which come from a variety of suppliers and whose MAs can vary in scope. Whilst the judgment by no means provides certainty that adopting the same colour as an originator will be lawful, generic inhaler manufacturers will be comforted by the fact that the court noted that there is "a sound medical rationale behind this practice of generics adopting similar colour schemes to the originator products, as it promotes familiarity amongst patients with their inhalers...and hence patient adherence to their drug regime".

As for originators who are looking to rely on 'soft' IP rights to protect their products following the expiry of the relevant patents, this case demonstrates the difficulties in succeeding on a claim in passing off. However, a claim based on a registered trade mark, or a registered design, may be a viable alternative with higher prospects of success. Originators will therefore no doubt continue to consider whether trade mark or design registrations could be obtained which might protect the 'look and feel' of their pharmaceutical products.

In the UK, GSK has sought permission to appeal the judgment, although this has been dismissed. GSK is also pursuing claims in other jurisdictions which relate to the same products.

¹ *Glaxo Wellcome v Sandoz & others* [2019] EWHC 2845 (Ch)

² Bristows acted in these proceedings for two entities within the Vectura group. The Vectura parties were joined to the proceedings in June 2018 as co-defendants with Sandoz, having been responsible for the initial development of the inhaler device used in the AirFluSal Forspirow

The interplay between the Clinical Trials Regulation and the GDPR



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The EU Clinical Trials Regulation (CTR) will likely become applicable in 2020, upon confirmation of the full functionality of the Clinical Trials Information System (plus an additional six months). With the implementation date approaching, in April 2019 the EU Commission published a list of 11 'FAQs' on how the requirements of the CTR interact with those of the EU's General Data Protection Regulation (GDPR). Given the critical significance of personal data in any clinical trial, it is hardly surprising that questions were frequently being asked. Neither legislation takes precedence over the other, and so those conducting clinical trials must ensure they achieve compliance with both regimes.

The FAQs were preceded by an Opinion, issued in January 2019, by the European Data Protection Board (EDPB). Both the Opinion and the FAQs provide a useful insight into the regulators' position, particularly as regards the appropriate lawful bases to process personal data relating to clinical trials.

The need for a lawful basis

For those less familiar with EU data protection law, any collection or use of personal data must satisfy one of the six 'lawful bases' set out in Article 6 of the GDPR. Where 'special category data' is processed, an additional lawful basis is needed, from the more restrictive list set out in Article 9. Since special category data includes health information (as well as ethnicity, sexual orientation, genetic and biometric data), it is to be assumed that at least some personal data collected in the context of all EU clinical trials will need a lawful basis under both Article 6 and Article 9.

Conducting a clinical trial in accordance with the CTR will require the processing of personal data for numerous purposes, including: to conduct the research itself;

perform safety reporting; archive the trial master file for 25 years as well as medical files of subjects for a period set by national law; and allow auditing, including of individual patient records, by national inspectors. All of these activities will involve a consideration of the ‘lawful basis’ relied upon, for the purposes of GDPR, by the sponsor/investigator institution (as the “data controller”).

When considering the various uses of personal data in this context, the FAQs and the EDPB distinguish between, on the one hand, processing relating solely to the research itself and, on the other hand, processing relating to the safety and reliability of the clinical trial.

What lawful bases to rely on?

The processing of personal data to ensure the safety and reliability of the clinical trial is a requirement of the CTR. Therefore the processing is necessary to comply with a legal obligation imposed on the data controller, and so the controller can rely on Article 6(1)(c). For an Article 9 condition, the GDPR legislators clearly envisaged these precise circumstances – providing the specific basis in Article 9(2)(i) of processing “*necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health or ensuring high standards of quality and safety of health care and of medicinal products or medical devices...*”

The research itself, however, is not derived from a legal obligation, and so will need a different lawful basis. The recommendation of the Commission and EDPB, for public authorities or those with a public mandate, is to rely on “*processing necessary for the performance of a task carried out in the public interest*” (Article 6(1)(e)). For those without a public mandate, the Commission and EDPB suggest ‘legitimate interests’, in Article 6(1)(f), as the most appropriate basis. To rely on the legitimate interests basis, the controller will need to conduct a balancing test between the legitimate interests identified (which could include wider societal benefits, as well as commercial interests) and those of the data subjects, to ensure its legitimate interests prevail. Again, the controller will also need an Article 9 basis – and the most logical will usually be that the processing is necessary for scientific research purposes.

A notable absence from the above is any discussion of consent as a lawful basis. It may come as a surprise to those not thoroughly immersed in the tangles of data protection law to learn that a controller can – and in many cases *should* – process personal data in clinical trials *without* obtaining the participant’s consent.

When is a consent not a consent?

The question of consent is, without doubt, one of the thorniest legal issues presented by the interplay between the GDPR and the CTR. The CTR requires the informed consent of the individual, as a fundamental condition for their participation in a clinical trial. However, both the Commission and the EDPB are keen to emphasise

that this ‘consent’ is entirely distinct from a consent to processing of *personal data*: it is in place to ensure the protection of two EU Charter rights, the protection of human dignity and the integrity of the individual. It is not an instrument for data protection.

In fact, quite the opposite is true. The Commission and the EDPB agree that ‘consent’, as understood in a GDPR context, will generally *not be* the appropriate lawful basis under which to process personal data in a clinical trial.

This is because of the stringent requirement, under GDPR, that any data protection consent must be “freely given”. In order to be freely given, there cannot be an imbalance of power between the data subject and the controller, or exist any other circumstance which might limit the data subject’s ability to exercise a genuine choice. The EDPB warns that where the participant is not in good health, belongs to a disadvantaged group, or is in a situation of hierarchical dependency, consent will be presumed to not have been freely given, and will therefore be invalid. An indigent cancer patient would not, realistically, be exercising a ‘free choice’ when deciding whether their personal data can be processed as a necessary condition to their receiving treatment.

The fact that a GDPR consent can be withdrawn also makes it a less attractive lawful basis for the controller: if a participant drops out of the trial and withdraws their consent to data processing, it would be very frustrating for the investigator to have to cease processing any of the data *already collected* for the purposes of the research (although the data could still be retained to comply with legal obligations).

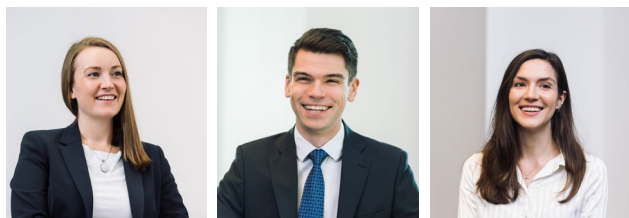
Since the distinction between a CTR consent and GDPR consent can be confusing enough to lawyers, controllers must work especially hard to avoid passing on this confusion to data subjects. The GDPR requires controllers to specify their lawful basis to data subjects, and so careful thought must be given when drafting informed consent forms and notices to ensure that they don’t mislead or confuse participants as to what they are ‘consenting’ to.

A Brexit Epilogue

A brief and unavoidable word on Brexit, since both the CTR and GDPR are EU laws. The UK has confirmed that the GDPR will remain in UK law, termed the “UK GDPR”. As regards the CTR, if implemented during the transition period introduced under the amended Withdrawal Agreement concluded between the EU and the UK (which is to end on 31 December 2020 unless extended¹), it will apply in the UK in its entirety. In any event, however, the UK Government has confirmed their intention that UK law will remain aligned with the CTR.

¹ Following the General Election of 12 December 2019, the new UK Government has pledged not to request any extension to the initial transition period

Cell and gene therapies: blockbuster prices and licensing challenges



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In recent years, we have seen a trend towards the launch of new gene and cell therapies with record-breaking price tags. Such headline-grabbing launches are becoming more and more frequent, as the pipeline for advanced therapies at all stages of development continues to grow at a rapid pace¹. We are also seeing industry and payers adopting new innovative pricing models for those products, such as outcome-based reimbursement and annuity payment models. In this article, we discuss these emerging alternative pricing models and consider the impact they may have on related licensing arrangements.

Current trends

AveXis, a subsidiary of pharmaceutical giant Novartis, recently announced that it had received approval from the US Food and Drug Administration to market its gene therapy Zolgensma for the treatment of paediatric patients with spinal muscular atrophy (SMA). Although this is the first promise of a cure for this debilitating and lethal condition, the media coverage has focussed instead on Zolgensma's price tag, which at \$2.1 million per patient makes it (currently) the world's most expensive medicine.

Zolgensma is illustrative of a general trend in gene and cell therapies that have reached the market in recent years and established a new standard of pricing for single-treatment medicines. While manufacturers point to the relative cost-effectiveness of such treatments (which may offer a one-off cure for severe conditions that otherwise would require several years' worth of conventional treatments and care) public and private payers are concerned about this new escalating pricing paradigm.

Health care systems may be able to absorb such high prices for rare diseases with small patient populations. However, the current reimbursement systems will be under severe pressure if (as is hoped) pipelines for advanced cell and gene therapies result in treatments for common conditions such as diabetes or heart disease. The Institute for Clinical and Economic Review in the US has estimated that if gene therapies are developed to treat only one in ten American patients with a genetic condition – approximately 1% of the total population – the cumulative budget impact could rise to \$3 trillion². For comparison, the projected total healthcare spend in the US for 2019 is \$3.8 trillion³.

Alternative Pricing Models

The pharmaceutical industry has sought to counter criticism over the high price tags for gene and cell therapies by coupling these revolutionary therapies with new and unconventional pricing and reimbursement mechanisms.

One alternative structure that has been adopted is an annuity based model which spreads the payment for an expensive treatment over several years in a pre-agreed payment plan, thus minimising the up-front cost to payers.

Another approach adopted by the industry, and perhaps an even clearer way to demonstrate value to payers, has been to tie reimbursement to patient outcomes. The industry has negotiated several of these outcomes-based reimbursement models with public and private payers for cell and gene therapies. Reimbursement payments to the drug maker under this model are conditional upon the patient reaching specific clinical outcomes by set deadlines. Depending on the model, a patient's failure to meet the specified clinical outcome can result in the drug maker having to refund payments received and/or forfeit any subsequent payments.

These new models are also being blended to create payment plans which combine annuity-style payments with rebates and outcomes-dependent instalments. We expect that in the years to come other creative payment models will emerge and be adapted from other therapy areas. For example, in Australia, the government has used a subscription style model that allowed it to pay a lump sum to drug makers for unlimited access for patients to curative hepatitis C treatments such as Sovaldi for a period of time.

Licensing Challenges

Cell and gene therapies often have their roots in academic research laboratories and the main players in this field of treatments have close ties and valuable licensing agreements with academic research institutions. For example, AveXis, the biotech company that developed Zolgensma, started as a spin-out to continue research conducted at the Center for Gene Therapy at

Name and manufacturer	Therapy type and indication	Initial list price in the US	Pricing model
Zolgensma by AveXis (subsidiary of Novartis)	Gene therapy for spinal muscular atrophy	\$2.125 million	Instalments over five years with outcomes-based rebates
Zynteglo by Bluebird Bio	Cell and gene therapy for transfusion-dependent beta thalassaemia	\$1.8 million	Instalments over five years dependent on outcomes
Luxturna by Spark Therapeutics	Gene therapy for inherited vision loss	\$0.85 million	Payment up front with outcomes-based rebates
Kymriah by Novartis	Cell and gene therapy for acute lymphoblastic leukaemia	\$0.475 million	Outcomes-based, payment after one month

Nationwide Children's Hospital in Columbus, Ohio. To further its spinal muscular atrophy work, the biotech also licensed a patent owned by Martine Barkats, a researcher at the Institut de Myologie, Paris. Shortly after, AveXis was bought by Novartis for \$8.7 billion. Cell and gene therapies such as Zolgensma will generally have more constituent parts (such as promoters, viral vectors and cell lines) than other more conventional small molecule therapies. This means that a party commercialising a cell or gene therapy will often need to license in more third party intellectual property or materials than a manufacturer of a conventional small molecule therapy. Most cell and gene therapies reaching the market are therefore likely to be underpinned by one or more licence agreements.

While much has been said about the impact of alternative pricing and reimbursement mechanisms on drug makers, payers and patients, we want to also consider the impact on licensors of the intellectual property which enables the development and manufacture of a therapy. In particular, how future pricing and reimbursement models can impact the royalties payable by licensees to their licensors. One inherent challenge is that these licences are generally negotiated many years before the commencement of discussions with payers on pricing and reimbursement mechanisms, making it very difficult to predict which scenarios will be relevant down the line. The positions of all of the stakeholders in the pricing debate are also constantly evolving, especially as data on the cost-effectiveness of annuity and outcomes-based models continues to accumulate. One factor which makes things particularly difficult for licensors in forecasting potential future royalty streams for these products is that a licensor would rarely have any involvement in negotiations regarding pricing and reimbursement so will have no control over the model adopted.

Annuity model challenges

Generally a licensor will only receive royalties once the licensee has itself received (or at least invoiced) payment from payers. An annuity payment model is therefore likely

to mean that royalties will also be paid in instalments potentially spread over a number of years following treatment of a patient. While in practice this may not be a large change for licensors to adjust to (as annual payments for these high price treatments are not out of line with other orphan drug costs, most of which need to be taken over a long period of time) there are also other factors to consider.

One concern that has been raised with annuity payment models is that there may be an increased risk of non-payment as over time licensees may face difficulties in collecting payments, for example because a payer stops complying with payment schedules or becomes insolvent. This may have the knock-on effect of reducing royalties due to a licensor. Licensors may seek to reduce this non-payment risk by asking that royalties are payable on sums invoiced by a licensee, rather than sums received (although this is likely to be resisted by a licensee or perhaps only accepted with caveats). Annuity-based models are also typically more complicated and more expensive for a licensee to manage administratively and those costs are likely to be deductible from sales totals before a licensor's royalties are calculated.

From a legal drafting perspective, care would also need to be taken by the licensor when defining payment terms and the royalty term (which is commonly linked to patent expiry) to ensure that the licensor continued to receive royalties in respect of patients who are treated within the royalty term, notwithstanding the fact that payment may not be received until after the patents and royalty term has expired.

Outcome-based model challenges

In relation to outcome-based models, a fundamental concern for both licensors and licensees is the uncertainty associated with a model which involves an upfront payment of the full treatment price but a refund payable some months or years down the line if the clinical outcomes are not met.

If royalties are payable on net sales of the therapy on a regular basis (e.g. quarterly or annually) then unless the licence includes a mechanism to take account of outcomes-based refunds made by the licensee to payers, the licensee could find itself out of pocket, unable to recover royalties paid to the licensor despite having had to refund the therapy price to the payer. To counter this risk, a licensee may seek to build in a royalty claw back mechanism into the licence, or to delay the point at which royalties are payable until after the relevant patient has met the required outcome. However, a licensor is unlikely to accept a significant delay in payment of royalties, particularly where the licensee has itself been paid. Academic licensors, with an obligation to invest income from technology transfer activities into research and the provision of education, are particularly unlikely to agree a royalty claw back structure which could force them to refund royalties or milestones a year or more after having received them.

One alternative option may be to agree that the licensee can make deductions against future royalty payments. A further alternative could be for some portion of the royalties paid to be retained in escrow for a period of time, to be released to the licensor upon achievement of a positive clinical outcome or expiry of a set period of time. However, escrow arrangements necessarily increase the complexity of agreements and are difficult to negotiate upfront when payment and reimbursement models and the associated outcome triggers have not yet been set.

A compromise?

As we have outlined in this article, although there are some things each party can consider at the outset of negotiating a licence, getting into protracted negotiations about hypothetical scenarios is unlikely to be attractive to either party.

The parties may wish to adopt an alternative approach of including robust governance provisions in the licence to deal specifically with this issue. For example, establishing a committee comprised of representatives of both parties to oversee and review issues relating to pricing and reimbursement. This may give the licensor a clearer oversight (and potentially input) into decisions which may impact future royalty streams and may present the licensee with an opportunity to propose alternative payment structures to support its desired pricing model. This could be combined with a mechanism for proposing and agreeing amendments to payment provisions in the licence if necessary to accommodate pricing and reimbursement issues which were unforeseen at the outset. Of course the success of such mechanisms will depend on the strength of the relationship between the parties and a combined willingness to work together and potentially compromise. It would also be important to ensure it is clear what happens where the parties cannot agree (e.g. escalation? expert determination?

preservation of the status quo?). However, in a future where pricing and reimbursement issues are only likely to become more complex and of key importance to the success of complex treatments such as cell and gene therapies, it will be interesting to see whether this is a route industry explores.

Conclusion

The launch in recent years of a number of advanced cell and gene therapies with blockbuster price tags has heralded a new era for drug pricing and associated payment and reimbursement issues. It is a trend that looks likely to continue if current pipelines can also deliver much anticipated advanced therapies for common conditions. The high prices associated with these products present a myriad of issues however, not only for patients, payers and healthcare providers, but also for the licensors of the underlying intellectual property underpinning such treatments as industry adopts innovative new payment and reimbursement models which may impact on royalty streams.

When negotiating a licence to technology underpinning a cell or gene therapy the parties should consider how less conventional pricing mechanisms may impact the royalty structure. However, while there are some issues licensees and licensors may be able to consider upfront, it is difficult to anticipate the issues that may become relevant at a stage where pricing models have not been set, particularly as there is no one-size-fits-all pricing approach.

We have proposed an increased use of robust governance processes in a licensing relationship as one option to consider. It will also be interesting to see whether any trends emerge in relation to upfront and milestone payments in response to the challenges outlined above. In particular, licensees may push for more back-loaded or performance-related milestone payments to reflect the risks associated with pricing models which take a longer term view of the cost benefits of these types of therapies. We look forward to seeing what innovative approaches licensors and licensees adopt to adapt to these challenges in the years to come.

¹ According to the Alliance for Regenerative Medicine (ARM), as of the end of 2019, there were a global combined total of 1,066 ongoing clinical trials for gene and cell therapies and tissue engineering therapeutics. The field of regenerative medicines is also continuing to receive extensive investment, with total global financings for 2019 amounting to \$9.8 billion: https://46ax7g7ngmq3divu13d9zsn1-wpengine.netdna-ssl.com/wp-content/uploads/2020/01/Janet-Lambert_ARM_Phacilitate-2020_FINAL2-1.pdf

² Institute for Clinical and Economic Review: <https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf>

³ Centres for Medicare & Medicaid Services: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/ForecastSummary.pdf>

Bristows' Genome Editing Debate 2019 : The Quest for the Perfect Human?

Last November, a week of international meetings to discuss global responses to the impact of gene editing began with Bristows' human genome editing debate, "The Quest for the Perfect Human?" held at the Royal Society.



In Paris, delegates at a meeting of the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) asked whether it was ethical not to adopt mosquito gene drives to conquer malaria, discussed public engagement, and considered the regulation of "GE" foods. Meanwhile, in London an International Commission on the Clinical Use of Human Germline Genome Editing convened by the Royal Society and US National Academies of Medicine and Sciences (NAM & NAS) heard evidence from scientists, clinicians and regulators from around the world, to help it to identify the scientific, medical, and ethical requirements to be considered when assessing clinical applications to undertake heritable human genome editing, if (and it's a particularly big if) society concludes that human germline editing applications are acceptable. In both Paris and London, where delegates were met by protesters opposed to the creation of "designer babies", the focus was upon the international governance of something which is prohibited almost everywhere, and barely discussed in the average kitchen: changing the germline genetic identity of human beings.

To raise the curtain on such an auspicious week, Bristows held a debate at the Royal Society featuring four eminent panellists, chaired by the distinguished broadcaster Joan Bakewell, and a hall of almost 300 guests, including the UK co-chair and members of the International Commission, members of the World Health Organization's expert advisory committee on the governance and oversight of human genome editing,

leading IVF experts, scientists and philosophers, representatives of patient groups, research funders, religious representatives, policy makers, life science businesses, regulators, a biohacker, an activist opponent, and senior lawyers. The event was provocatively entitled "The Quest for the Perfect Human?".

Dr Helen O'Neill, a molecular geneticist working in the field of genome editing, opened the debate with a fresh appraisal of the superstar gene-editing tool, "CRISPR" that had triggered so much excitement and concern. Fearlessly zoning in on the technical meaning behind the famous acronym, Dr O'Neill considered how those "Clustered Regularly-Interspaced Short Palindromic Repeats" of DNA might inform debate over its use.

It certainly wasn't new or artificial: far from being invented in 2012, CRISPR is billions of years old. Its human significance arose, first, from the realisation that those weird palindromic repeats in bacterial DNA are part of an ancient immune system that recognises, then cuts up, the DNA of viruses¹. Second, and most decisively, was the brainwave that CRISPR could be used to seek out and slice any piece of DNA in any living organism so as to change its genome, and thus the fundamental character of cells, tissues and organisms. Third, edited DNA need not only affect one organism, but its descendants, too; indeed, entire populations. Such "germline editing" implied something especially profound to us as humans. It might soon be possible for carriers of genes for conditions such as Huntington's disease to have healthy children using their own gametes (sperm and eggs), and for these children also to have healthy children. Dr O'Neill emphasised that the technology was by no means perfect, with problems such as "off-target" effects and, in the case of embryonic interventions, "mosaicism" (where only a proportion of the organism's cells are edited), but advances such as "base" and "prime" editing were reducing these risks sharply.

While clinical application is certainly premature, Dr O'Neill remarked that the genomic perfection implied by the title of the debate would always be a pipe dream. Not only is DNA inherently prey to mutation², but genomes can be affected in other ways (IVF is a strong candidate). Returning to the question under debate, she reminded the assembly that the issue in hand primarily concerned human behaviour, not science. Passing the subject to her fellow panellists, Dr O'Neill cited the remark of a former president of the Royal Society, Sir Isaac Newton, that he could "... calculate the motion of heavenly bodies, but not the madness of people."

The second speaker, the biologist Dr Nessa Carey, who is also author of "Hacking the Code of Life", now turned the discussion to some of the ethical issues confronted by germline gene editing. Reflecting on the dim borderline between disease avoidance and genetic enhancement, Dr Carey challenged the idea that it is up to society to decide which conditions should or should not be treated (as distinct from the question as

to whether human germline editing should be allowed at all). Should it not be the very individuals who live with particular genetic conditions who are consulted?

They are the ones suffering from the hereditary disorders and seeking treatment. Dr Carey illustrated her viewpoint by giving the example of those deaf communities which consider their condition to be socially beneficial and which challenge whether being a carrier for congenital deafness is really a condition capable of being “treated” by germline genome editing or any other means. Should the views of such communities, or of society at large, prevail over those of individuals wishing to have a healthy child? A rhetorical question that often arises in discourse on germline editing is, “what right do we have to intervene in the human genome?” Dr Carey flipped it: what right do we have not to intervene? If the technology is available to treat and prevent certain heritable conditions, then why should we not improve the life quality of our future children? What ethical objection would oblige us to leave them to incur lifetimes of genetic disease that could have been prevented? Why, indeed, does society lend such a special status to our genomes when it comes to editing them, despite the fact that we regularly subject our bodies to external influences that alter our DNA?

“What right do we have to intervene in the human genome?”

The next panellist, Professor Robin Lovell-Badge, head of the Laboratory of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute, turned to the issue of how human genome editing might be regulated. Professor Lovell-Badge is a member of the [World Health Organization’s expert advisory committee on the governance and oversight of human genome editing](#), which is examining the scientific, ethical, social and legal challenges associated with both germline and somatic⁴ genome editing, such as concerns about regulatory and governance gaps, rogue clinics exploiting those gaps (as many “stem cell clinics” still do in poorly regulated territories), and other inappropriate use. The WHO Committee aims to provide global recommendations for national consideration on the subject of appropriate governance mechanisms. One recent suggestion, which followed the [He Jiankui CRISPR baby scandal](#) that had occurred almost a year before the Bristows debate, was a [call for an international moratorium](#) on the clinical use of human germline editing, a proposal urged, among others, by Professor Lovell-Badge’s fellow WHO Committee member, the distinguished Canadian bioethicist and philosopher Professor Francoise Baylis, who was also in the hall. Professor Lovell-Badge felt that the moratorium would be ineffective: without national enforcement powers, no moratorium could prevent the kind of experiments performed by He Jiankui.

CRISPR moves quickly. A week after Bristows’ Royal Society debate, [CRISPR Therapeutics](#), the company founded by CRISPR co-inventor, Professor Emmanuelle Charpentier and our final speaker, Dr Rodger Novak, [announced](#) highly positive interim data from the first two patients with sickle cell disease and with beta thalassemia to be treated with CRISPR-based therapies⁵. The possibility that CRISPR might cure such serious haemoglobin disorders just 7 years after Professor Charpentier’s breakthrough paper with Professor Jennifer Doudna is truly astounding, yet it was this exact hope that had driven Dr Novak and Professor Charpentier to start their company. Dr Novak hadn’t even known what CRISPR was when Professor Charpentier called to tell him about it, but since then their company has grown astonishingly, founded on the hope that previously untreatable conditions could yield to the new method. So, does the apparent power of somatic editing mean that non-heritable editing is an “ethical alternative” to germline intervention? Dr Novak would not be drawn on this. However, he did raise the immense costs involved in developing marketable products, which spoke to issues of access and reimbursement affecting gene therapies in general. Furthermore, the quality and safety standards being developed for gene-edited medicinal products were of obvious value to those working on appropriate standards for heritable interventions.

After speeches from the podium, the Chair invited questions and submissions from the floor. These included observations by patient groups, the above-mentioned Professor Francoise Baylis, Professor Dame Kay Davies (co-chair of the International Commission), Professor David Albert Jones of the Catholic Anscombe Bioethics Centre, a self-described biohacker and an activist opposed to genetic interventions in general. Although no objections to somatic editing were raised, concerns were raised in connection with germline interventions, with one delegate calling for an international agreement to ban specified (but unidentified) edits. Two striking concerns were access and inequality. Moreover, a sense of proportion was also needed: yes, genome editing could lead to inequalities, but didn’t the world have far greater ones to deal with? The responses of the panellists were framed by the assertion, voiced by Dr Carey and Dr O’Neill, that the opinions of patients are of primary importance in the genome editing conversation.

The debate drew to a close after [Sarah Norcross](#), Director of the Progress Education Trust, brought the panellists back to the inflammatory question that had brought them there. Could human genome editing merely be a quest for “the perfect human”? Panel members were repelled by both the scientific absurdity and political toxicity inherent in the question. Dr Carey recoiled against the very premise that humans could be perfected, identifying this with notorious historical practices exercised by those in power to privilege their own ideal of human perfection to the detriment of humans lacking it. Professor Lovell-Badge suggested that, within the

existing legal framework (which forbids interventions for eugenic purposes), the power to edit genomes would give individuals more choice over who should be born, not less. Finally, Dr O'Neill emphasised that the idea was scientifically ridiculous: genomes can never be “perfect”, and people are not defined by them. Her identical twin, for example, had developed quite differently, as a lawyer. These things happen.

Bristows' lawyers have supported innovators for over 180 years, routinely working at the point where cutting edge technologies clash with regulations blunted by age. Genome editing is one of many areas in which our lawyers have deep expertise and concern for the proper development of the law. Fostering an environment from which responsible and better-adapted regulations and governance systems may ultimately arise seems the right thing for us to do.

Let the debate continue.

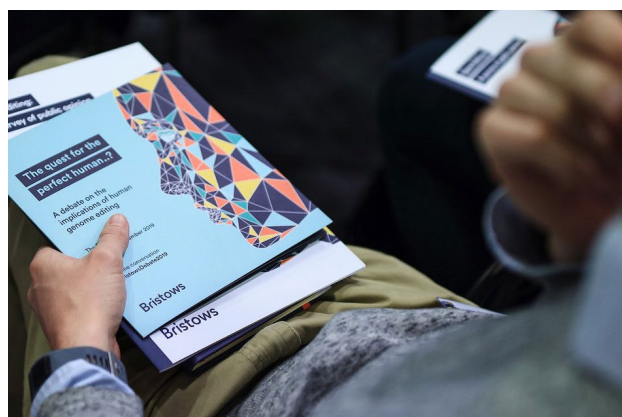
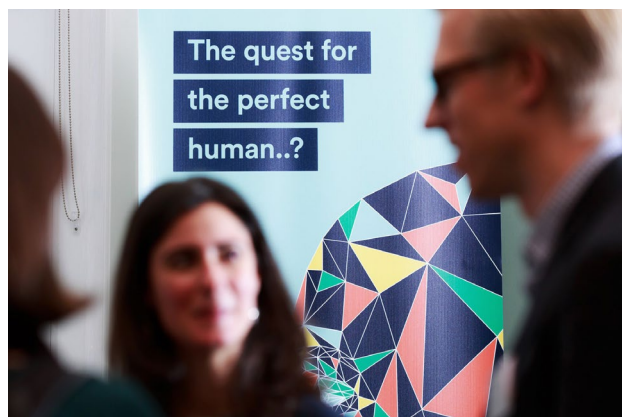
¹ Bacteria get infections, too. “So, naturalists observe, a flea has smaller fleas that on him prey; And these have smaller still to bite ‘em, and so proceed ad infinitum.” Jonathan Swift (1733)

² Life evolves by the selection of random mutations: no mutations, no evolution

³ The following day at the meeting of the International Commission, a speaker called for a clear list of conditions

⁴ i.e. non-heritable interventions aimed at the cells of a person or foetus

⁵ In ongoing Phase 1/2 clinical trials conducted with Vertex Pharmaceuticals Inc.



CRISPR and the implications of human genome editing



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In 2012, Science published a paper on bacterial immune systems, which, the authors remarked, could be used to make precision edits to DNA in living organisms, thereby changing their genes and characteristics. Although 'genome editing' technologies were not new, the bacterial system, named 'CRISPR', offered a much faster, more accurate and cheaper method of hacking the code of life, with an apparently limitless power to modify the living world, and ourselves.

That CRISPR should appear at a time of unprecedented global challenges, including climate change, energy shortage, food security, species extinction, population growth and degenerative disease, each of which could, in principle, be ameliorated by the use of CRISPR, seemed especially fortuitous. It might, for example, be used to produce more productive, drought-resistant crops, chunkier livestock, and to eliminate disease-bearing insects. It might also be used to engineer better gene therapies, and to prevent the inheritance of genetic disorders in humans, such as Duchenne Muscular Dystrophy. Unsurprisingly, such a revolutionary technology has raised profound ethical, social, commercial and regulatory concerns, particularly in the human context, and no more so than in the case of 'heritable genome editing', where changes to a person's genome are passed on to future generations. Though it is not yet sufficiently developed to be carried out safely with confidence, and is illegal in around 30 countries (including the United Kingdom), law makers may soon have to decide whether to permit heritable genome editing.

The issues are daunting. Although its therapeutic use might reduce the burden of heritable diseases, some fear that CRISPR might be exploited unethically, and that the distinction between disease avoidance and enhancement may be difficult to draw. While 'transhumanists' believe that genome editing should be used to accelerate the evolution of brighter, fitter human beings, others respond that their discourse devalues people and promotes inequality. Even without transhumanist idealism, could genome editing deepen social differences between those who are able to afford it and those who are not? How significantly might it exacerbate social inequality? How seriously should we take the possibility of a 'genetic elite' emerging with social and legal privileges?

A contrasting concern asks whether commercialisation of genome editing (now in its early stages) could lead to monopolisation of the technology by small numbers of companies, impeding innovation. Could the control of the technology by such a small group further contribute to social inequality?

One question stands out. Should we permit human heritable genome editing at all, and if so, on what terms? The global ethical consensus is, for the present, opposed. Opposition deepened when, in November 2018, a Chinese researcher, He Jiankui, announced that he had used CRISPR to edit human embryos to make them HIV-resistant, and that two of them were now baby girls. His announcement was met with near-universal condemnation. In response, a group of leading scientists called for a 'global moratorium' on human heritable genome editing. Despite the good intentions of their declaration, can it actually prevent the actions of another He Jiankui? Or should we instead embrace the international efforts, now being led by leading academic and public health institutions, to identify global standards of clinical practice and governance of human genome editing? Or perhaps heritable editing is a red herring of limited clinical or commercial interest, and we should be paying more attention to the use of CRISPR in developing personal medicines, instead?

Gene editing technology has given us unprecedented power over the genetic destiny of living species, including our own. But with power comes responsibility and, ultimately, the design of laws.

DIY gene-editing CRISPR kits: Enabling biohackers to evade the eyes of the regulators?



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What are DIY gene-editing kits?

In the few short years since its discovery, CRISPR-Cas9 has transformed bioscience like no other invention in the last half century. Already the most common technique of gene editing, CRISPR works like a satnav system joined to a pair of molecular scissors. It is essentially a couple of enzymes that can be designed to find and remove a specific strand of DNA inside a cell, and then replace it with a new piece of genetic material. CRISPR can be used to rewrite single letters of genetic code and even whole genes, and improvements such as “base editing” and “prime editing” are increasing its accuracy and reliability. It could make a significant impact on the global challenges of food security, climate change, energy, as well as in the domain of animal and human health, and the fight against antibiotic resistance (discussed [here](#)).

Editing genomes is immensely difficult, but as prices drop and gene-editing expertise becomes more accessible, DIY CRISPR kits have become freely available online for as little as 159 USD. They enable citizen scientists, including so-called “biohackers”, to solve problems that have foxed the professionals, make genetic discoveries, much as amateur astronomers add to the tally of known exoplanets, and devise novel applications. One such kit, on sale by The Odin, a company founded by biohacker and ex-NASA scientist Josiah Zayner, is said to contain everything needed to make precision genome edits in bacteria, all in the comfort and privacy of one’s own home (or garage).

DIY kits such as these have limited applications. They can make bacteria and yeast change colour, produce a fragrance or live in inhospitable places, but their lives are short. It’s claimed that they only work in prokaryotic (i.e. bacteria and archaea) cells and in yeast. But yeast, like us, is a eukaryote, so the possibility of altering human genes or producing glowing cats is at least theoretical. So could the private use of these or future DIY kits pose a risk to the environment or to human health? Could biohackers become skilled enough to introduce genes into the biosphere for nefarious purposes, creating dangerous pathogens, for example? The risk from amateur editing certainly appears low, but it is not zero, and it is magnified according to the number of kits in use. Is the law up to the challenge of such a powerful and disruptive technology?

The UK’s Nuffield Council on Bioethics investigated biohacking as part of its wider report on the implications of advances in gene editing in 2016 ([here](#)). It found that European DIY biology is “*considered to be better or more consistently regulated than its US counterpart*”, but concluded that new gene-editing techniques could be “*game-changing*” in the way they enable “*non-institutional actors*” to participate in cutting edge bioscience. This was prescient. The following year, two American biohackers attempted DIY gene therapy on themselves. The first injected himself with an untested gene therapy for HIV; the second aimed to knock out the myostatin gene using CRISPR, a genetic change associated with increased muscle mass. Both men livestreamed the procedures on the internet. Both procedures failed. The US Food and Drug Administration (FDA) then took a stand against such CRISPR kits for DIY (supposed) gene therapy, but biohackers argue that the biomolecular components of DIY gene therapy, such as CRISPR plasmids and guide RNAs, are not inherently dangerous by themselves and can be acquired perfectly legally. In any event, the very nature of self-administration is difficult to regulate and enforce against, and livestreaming is not compulsory. Even if the DIY kit and any domestic “therapeutic” product it might create were caught in the regulatory sieve, who would know?

Could it happen in the realm of human germline genome editing (hGGE)? We may get an inkling from the reaction to the astonishing and unwelcome boast of the Chinese biophysicist He Jiankui, that he had created the world’s first genetically edited babies. Calls for strict regulation swiftly moved up the international agenda, with some calling for an international moratorium on hGGE. The focus was on the development of international standards for hGGE, and on the conduct of hGGE researchers operating within scientific institutions. Setting standards is undoubtedly an urgent and important enterprise, but a scientist who goes on a frolic of his own, as He Jiankui did, would probably go undetected. If He Jiankui had implanted edited human embryos in the UK, he would have acted in contravention of the Human Fertilisation

and Embryology Act 1990. But who would know? It's extremely unlikely that any currently available editing kit is likely to facilitate hGGE, but things could change, and attempts could easily evade the eye of the law.

Editing human germlines may be less exciting to geeks than hacking animal and plant genomes, an activity which has abruptly become heavily regulated: too heavily, some would say. Again, the mote in the eye of the regulations is the assumption that altering genomes is the exclusive preserve of institutions and well-behaved scientists. Could the irrationality of these laws tempt those on the fringes to breach them behind closed doors?

Prior to the discovery of CRISPR in 2012, the EU implemented regulations for the deliberate release of "genetically modified organisms". That's a legal term: the GMO Directive (Directive 2001/18/EC) defines a "GMO" as "*an organism...in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*". In July 2018, the Court of Justice of the European Union (CJEU) ruled that products of "directed mutagenesis" (i.e. of an endonuclease editor such as CRISPR-Cas9) are "GMOs", and regulated to the fullest extent as such¹. The decision has been widely criticised for failing to place edited organisms under the Directive's clear exemption for products of mutagenesis, leading to the ironic result that organisms derived by random mutagenesis are exempt from the strictures of the Directive, while those created by precision mutagenesis are not. The UK implements the GMO Directive in its Genetically Modified Organisms (Contained Use) Regulations 2014 (GMO Regulations), which state that a "*person responsible for the contained use must ensure that a suitable and sufficient assessment of the risks to human health and the environment created by the use is carried out*". This is a considerable burden, and the competent authority has the power to require any user to suspend, terminate or not to commence a particular contained use which has been notified to them under the GMO Regulations. It carries the same maximum penalty as under the Health and Safety at Work etc. Act 1974: six months imprisonment, an unlimited fine, or both. In response, crop scientists and others claim that the GMO Directive is being construed in a way that neglects scientific evidence, is wholly disproportionate to any likely harm, and fails to reflect the danger of impeding the development of organisms having positive human and environmental effects, notably CRISPR-Cas9. New legislation has been urged, but until it appears, if ever, the present regulation is challenging. Except, perhaps, to biohackers. The regulatory powers ultimately depend on notification by the user to the relevant authorities. Would biohackers feel obliged to comply? Who, really, is going to find out that those delicious tomatoes were engineered in a potting shed?

The GMO Directive is in large part a child of the millennial Cartagena Protocol on Biosafety to the Convention on Biological Diversity (Cartagena Protocol), Article 16(3) of which requires signatories to take "*appropriate measures to prevent unintentional transboundary movements of living modified organisms*". Following the CJEU's decision last year that gene-edited organisms are GMOs for purposes of the GMO Directive, the same has become true for Cartagena purposes. Do Cartagena signatories in Europe now have a precautionary duty to regulate domestic kits in order to prevent transboundary movements? The US is not a Cartagena signatory, but some US scientists have argued for rules to reduce the likelihood of a bioengineered "super-microbe" escaping from the lab or being deliberately unleashed. Should these extend to the world of the biohacker, and if so, how? Would this even be feasible?

What's next in the regulatory landscape for these DIY kits?

It remains to be seen what else regulators and law-enforcement agencies will do to try to contain the ambitions of DIY biologists operating outside conventional scientific environments, especially those who stray into procedures that could affect the environment, are used as medical treatments or developed as weapons.

For now, the only real thing stopping determined people from modifying organisms (human and non-human) is the fiendish complexity of the process. Indeed, the European Centre for Disease and Prevention and Control (ECDC) has placed assessing the risks posed by DIY gene editing kits on the backburner, particularly in light of more pressing gene-editing issues. It has, however, advised that the risk assessment should be revised, should further information indicate that the distribution of such DIY kits extends more widely across the EU. Clearly, this is a developing area, with wide-ranging consequences, and may lead to more regulation when the use of such kits becomes more widespread.

¹ Case C-528/16 *Confédération Paysanne* EU:C:2018:583

Gene editing: A survey of public opinion



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Since the CRISPR breakthrough in 2012, genome editing has been the focus of a huge amount of attention and debate, thanks in part to its incredible potential: delivering personalised medicines, and preventing the inheritance of genetic conditions.

Human genome editing is prohibited virtually everywhere. However, such is its promise that the international scientific and medical establishments have begun to turn their minds to the clinical standards and governance frameworks that would be needed if it were to become lawful. Whether it ever does will depend on how the public responds to truly epic questions of bioethics:

- Should we allow the implantation of edited embryos to prevent them suffering serious genetic disease once born?
- Should we allow it for the purpose of benefitting future generations? Why not for the purpose of “enhancing” human characteristics?
- Could genome editing deepen social divisions?
- What are the dangers of commercial monopolisation?
- How can we avoid potential harms?
- What, in fact, does society in general think about all of this?

With regard to the last question, in May 2016, researchers from Australian universities published the results of a global survey on attitudes towards gene editing. Their report shows popular support, with around 60% of respondents “agreeing” to the use of gene editing to cure life threatening and debilitating diseases including via germline editing (editing the embryo). However, support for its use for non-health related purposes, like

selecting eye colour or intelligence, drops substantially (around 30%).

Three years and several CRISPR-driven gene editing developments later, we decided to see if public opinion on the topic has changed, and if so, how. One event seemed likely to have provoked public reflection. In November 2018, the Chinese physicist He Jiankui announced that he had successfully edited human embryos to disable a specific gene, attempting to make them immune to HIV, and that two such embryos were now healthy baby girls. His announcement was widely reported on by global media, and lambasted by many in the scientific community who condemned embryonic editing or considered his methodology to be unethical, and who supported an international moratorium. The incident also excited more general debate over human germline editing. Does the general population agree with the scientists?

Published in November 2019, our survey report has been used as reference content for a UK Parliament POST note about human germline genome editing in January 2020.

To check whether the debate had reached the wider audience, and with the permission of its authors, we replicated their research in the United Kingdom, using a nationally representative sample of the general population. We used Censuswide to run the survey.

The Results

What we found is that public opinion is still split: nearly half of the respondents agree with the use of genetic editing to cure debilitating and life-threatening diseases, around a fifth are neutral and around a tenth disagree.

The numbers do not change much when respondents were asked about gene editing in embryos. We could interpret this to mean that when it comes to diseases that seriously affect or threaten lives, people don’t feel strongly if the gene editing procedure is done on one individual only or on the germline. Instead, they appear to focus on the technique itself and on the reasons for using it. In contrast, the general opinion is turned the opposite way when it comes to using gene editing to change non-disease characteristics.

Only one in five respondents agreed with genome editing to alter physical appearance, intelligence or sporting ability, and almost half of the respondents are against it. If popular opinion is consistent across the world, as the 2016 research found, this would mean that regulators could, in principle, draw a clear line demarcating what is allowed in human genome editing and what must ethically remain off limits. Respondents to our survey widely rejected eugenics, while allowing genome and germline editing for the purpose of saving and improving the lives of people with genetic conditions.

Interestingly, this trend was consistent no matter if respondents identified themselves as religious or non-religious. Perhaps unsurprisingly, higher levels of education tend to correlate with people being more agreeable about the use of clinical gene editing techniques. This is also in line with the findings from the 2016 research.

We hope that this report serves as a prompt for all the actors involved: scientists developing new gene editing techniques, associations and companies in the sector, governments and intergovernmental entities regulating this field, patients who look to the clinical promise of genome editing, and the media writing about the topic – to keep talking openly and objectively about genome editing and its powerful potential, in order to fuel a healthy debate.

The full report is accessible on the Bristows main website [here](#).

Brexit is upon us – what does it all mean?



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Following the UK's referendum on continued membership of the EU in June 2016, and after a number of false dawns (the authors are avowedly and unapologetically pro-remain), extensions, suggestions of second referendums and parliamentary intrigue, the result of the UK's general election in December 2019 meant that the UK left the EU on 31 January 2020. We reflect on some of the obvious legal ramifications for those operating within the life sciences sector.

Stage one – the present

Stage one of 'Brexit' involves a standstill transition period as provided for in the amended Agreement on the Withdrawal of the UK from the EU dated 17 October 2019 ("the Withdrawal Agreement"). This period will last from the date the UK left the EU, i.e. 31 January 2020, until 31 December 2020, although there are provisions in the Withdrawal Agreement for the parties to agree a one-time extension of the transition period for up to 1 or 2 years. Nevertheless, the UK Government has indicated on numerous occasions that it has no intention to extend the transition period.

During this transition period, virtually all EU law¹ (the *acquis communautaire*), including in relation to pharmaceuticals, shall continue to apply to the UK in full even if the UK is not formally part of the EU. For example, all unitary IP rights and regulatory approvals extend to the UK, all harmonised EU law continues to apply to the UK (including IP, regulatory, competition and data protection law), and free movement of goods (including rules on exhaustion of IP rights) and workers continues to apply. To all intents and purposes the UK retains the benefits of EU membership during 2020.

Stage two – the future

Readers should not assume that all uncertainty has been swept away. As noted above, the transition period is relatively short, and the UK Government has already indicated it has no intention of requesting or agreeing to an extension beyond 31 December 2020 (which would in any event have to be agreed by 1 July 2020). Indeed, the UK Parliament has legislated at the Government's request so as to make it unlawful for the UK Government to request an extension although of course this legislation can just as easily be overturned if the need arises. The purpose of the transition period is to allow the UK and the EU to negotiate a future international relationship, which was not possible whilst the UK was still a member of the EU.

The UK and EU have agreed in parallel a set of political declarations ("the Political Declarations") as to the nature of this future arrangement, although it should be noted that these do not have the specificity of the language of the Withdrawal Agreement itself, are not binding and are not always in accordance with statements made since by the UK Government.

It therefore remains to be seen what form this future relationship will take. At this stage it is not possible to provide an analysis of the legal implications of the potential future agreement. However, one thing is worth bearing in mind. The UK Government has indicated that it is confident that an agreement can be concluded within the 11 short months between departure from the EU and the end of 2020. Not all commentators, nor indeed the EU, share this enthusiasm. The UK Government has also indicated that it will be able to negotiate a major free trade agreement with the US within the same period. It is not inconceivable that the UK will fail in the former, notwithstanding stated enthusiasm on the part of the UK and the EU to avoid a future 'hard Brexit'. No assumptions should therefore be made that the transition period will end on 31 December 2020 or that a new trading relationship with the EU will be in place before the UK exits the quasi-EU membership status it retains during the transition period.

What is known is that the UK Government has published its negotiating mandate for the UK's future relationship with the EU². This is not as ambitious or as harmonised as many in the industry would have liked and could lead to increased costs, trade friction and additional regulatory requirements for many sectors, including biotech. The EU has also published its draft negotiating directives³. Time will tell what this means for a potential UK – EU agreement.

In parallel, the Government has also published the Medicines and Medical Devices Bill 2019-21⁴, which is intended to create delegated powers covering the fields of human medicines, clinical trials, veterinary medicines and medical devices so as to update UK regulatory law following the departure of the UK from the EU.

As currently drafted, these create wide-ranging powers to amend legislation from 2021, albeit with limited guidance as yet on the UK's proposed future approach, including in a 'hard Brexit' scenario. It seems all bets are off for the time being, although it does seem that full harmonisation is no longer on the table.

¹ The exceptions are extremely limited and not of interest here

² <https://www.gov.uk/government/publications/our-approach-to-the-future-relationship-with-the-eu>

³ <https://ec.europa.eu/info/sites/info/files/communication-annex-negotiating-directives.pdf>

⁴ https://publications.parliament.uk/pa/bills/cbill/58-01/0090/cbill_2019-20210090_en_1.htm

Quick Facts

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

Our clients come to us for **advice** on a wide spectrum of **IP issues** including patents, trade marks and licensing, freedom to operate opinions, collaborations, mergers and acquisitions, financings and the coordination of disputes in multiple jurisdictions.

Our clients range from **multinational** pharmaceutical and biotech companies and medical device manufacturers to universities, SMEs and technology start-ups, private equity and venture capital investors.

The Bristows' life sciences team is among the **largest in Europe** comprising 23 partners and 45 associates, many with backgrounds in chemistry, biochemistry, engineering, genetics and neurosciences as well as law. They include some of the UK's **leading** practitioners in this sector.

Please take a look at our Life sciences microsite, On the Pulse, at www.bristowsonthepulse.com



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Greg is a contentious IP specialist whose advice extends across all industries, with a particular focus on patent litigation in the life sciences sector. This has included coordination of parallel litigation in a number of cross-border IP projects. He also advises on wider issues relevant to the life sciences sector.



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