

BRISTOWS

BIOTECH REVIEW

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Introduction

Dear readers,

Welcome to the latest edition of Bristows' Biotech Review. As with previous editions, our aim is to update you on some of the most important and influential developments affecting the biotech sector in the last 12 months, and to look forwards to those matters likely to affect the industry in the short to medium-term future.

The last 12 months have certainly been a busy and challenging period for the life sciences sector. On the positive side, we are seeing progressively more innovative technologies reach the market, with the prospect for game-changing patient treatment. In this edition, we include a review of CAR-T technology, following approval of the first two treatments in this class at European level.

On the negative side, no review would be complete without a nod to Brexit, and the significant impact it could have on the life sciences industry in the UK and abroad. At the time of writing, the EU-UK Withdrawal Agreement has been rejected three times by the UK Parliament and would appear to have reached the end of its road, at least in terms of the accompanying political declarations as they currently stand. However, the EU has agreed a short extension of the Article 50 notice period, by two weeks to 12 April 2019, to give the UK further time to approve the Withdrawal Agreement. With the political landscape changing by the day, outlining the future legal framework for the industry at times feels like an exercise in gazing into a crystal ball, only to have the ball fog over every couple of days. Nevertheless, we have tried to capture the key elements of the most likely future positions if the UK does leave the EU, being either: (i) a departure with no agreement in place; or (ii) the arrangements of the transitional Withdrawal Agreement. Readers will not be surprised to learn that the former will have a more dramatic impact than the latter.

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



Gregory Bacon
Partner
gregory.bacon@bristows.com

Greg is an experienced IP and regulatory lawyer with a particular focus on the life sciences sector. His extensive scientific background gives him a valuable understanding of technical issues that can underlie IP and regulatory matters. He has advised and represented clients on small molecule pharmaceuticals, biologics (originators and biosimilars), medical devices (traditional and software), as well as in the chemicals, technology, shipping and online publishing sectors.

Greg's particular focus is on patent litigation. He has extensive experience of acting before both the English High Court and Court of Appeal. In addition, Greg has widespread experience of strategic multinational litigation in multiple jurisdictions, including at the EPO, through global pharmaceutical product coordination projects for many clients. He also provides regulatory advice on the legislative frameworks governing pharmaceuticals and medical devices, both at EU and national level.

Greg has spent time on secondment to the IP litigation department of a leading IP law firm in the Netherlands as well as the UK legal department of a leading global healthcare IT company, working on non-contentious IP/IT, regulatory and commercial matters.

Figures

Biotech landscape in Europe and the UK

The UK raised a record £2.2 billion from investors in 2018. The figure is the highest ever recorded and almost double that raised in 2017.

(Source: The UK BioIndustry Association 2019)

In 2018, across Europe, UK companies accounted for 40% of all biotech venture capital raised and 45% of funding raised through IPOs.

(Source: The UK BioIndustry Association 2019)

In 2019, biotech is forecast to represent 27% of the global market, and by 2024, 31%.

(Source: Deloitte 2019 Global life sciences outlook)

Five UK biotechs launched on the public markets in 2018, this is the same number as in 2017 but the ticket sizes were larger, totalling £432.28 million.

(Source: The UK BioIndustry Association 2019)

There are now 1,229 Biotech companies in the UK. Other Sercives and Suppliers, Diagnostics and Analytical Services and Therapeutics make up the majority at 23.3%, 20.6% and 16.4% respectively.

(Source: UK Biotech database)

CART-T therapy market is projected to increase at an annualized rate of over 51% during the time period, 2018–2030.

(Source: Deloitte 2019 Global life sciences outlook)



Patent Litigation

Patent Litigation at Bristows

The majority of Bristows' IP lawyers have scientific or technology backgrounds, including biochemistry, biotechnology, genetics, neuroscience, chemistry, electronics, engineering, physics and material sciences. We actively recruit trainees who are First Class, and even PhD level, scientists from leading research institutions. This means that whatever the technology on which a client has built its business, Bristows will have someone with relevant background and experience.

Pregabalin – The Ruling of the UK Supreme Court



Brian Cordery
Partner



Claire Phipps-Jones
Senior Associate



Adrian Chew
Associate



Emma Muncey
Associate

This article was first published in Kluwer Patent Blog, November 2018.

In November, and after nine months of waiting, the decision of the UK Supreme Court in the pregabalin litigation was handed down. Like Brexit and the nation, it is clear that the Supreme Court Judges were divided on several crucial issues.

The background to the case is well known. Warner-Lambert had a patent with Swiss-type claims to the use of pregabalin in the treatment of pain (the "Patent"). The Patent had subsidiary claims to the use of pregabalin in inflammatory pain and neuropathic pain. Following the expiry of the compound patent for pregabalin in spring 2013, various generics companies wanted to sell pregabalin for non-patented indications including epilepsy and general anxiety disorder. However, the law was unclear as to what additional steps the generics companies should take, besides carving out pain from their label, to try and ensure that their pregabalin medicines were not used for the treatment of pain whilst the Patent was in force. In addition to taking such steps, the generics companies also sought to revoke the Patent and thus clear the way ahead of sales of their medicines for the treatment of pain. Warner-Lambert denied that the Patent was invalid and alleged that the Patent was infringed.

At first instance, Arnold J had held that the main claims of the Patent were invalid for lack of sufficiency and that in any event, they were not infringed. A post-trial application to amend the Patent to peripheral neuropathic pain was not permitted as it was held to be an abuse of process.

In the Court of Appeal, Arnold J's findings on validity were substantively upheld. However, the Court considered that the correct approach to the issue of infringement was that an objective intention test should be applied, and that a generic could in principle be liable for infringement if it could reasonably foresee that some of its product could be used for the patented purpose. However, the Court of Appeal held that a generic could escape liability if it had taken "all reasonable steps" to ensure that its medicine was not intentionally administered for the patented indication.

The Supreme Court's ruling considered four issues: (i) construction of the claims; (ii) abuse of process; (iii) sufficiency of disclosure and in particular the question of plausibility; and (iv) (obiter) the correct test for infringement of Swiss-type claims to the use of drugs in medical indications.

Construction

Lord Briggs (with Lords Reed, Sumption and Hodge agreeing) followed both Arnold J and the Court of Appeal in holding that "neuropathic pain" means all neuropathic pain, and not only peripheral neuropathic pain. Lord Briggs explained that validating construction, the idea that, where possible, a construction should be preferred which results in the relevant claim being valid, does "not usually have a significant place in modern patent law" and "would cut across the legal policies underlying patent protection". He also noted that, for second medical use claims, there is a particular need for legal certainty and that issues of construction should be addressed, as far as possible, by deciding "what it really does mean". It seems that Lord Mance was not quite as confident about this construction as the other Lordships. However, ultimately he also agreed.

Abuse of Process

The Lordships unanimously agreed with the Court of Appeal and Arnold J that post-trial amendments resulting in a new claim that had not been adjudicated on at trial were not allowed. Lord Sumption stated that the submission made by Warner-Lambert came "nowhere near surmounting those steep hurdles" for the Supreme Court to interfere in procedural points. In any event, as will become clear in the following paragraph, contrary to the findings of the lower courts, the Supreme Court held that the proposed amendments would not have saved the Patent.

Sufficiency

The issue of plausibility also saw their Lordships split in opinion. The majority favoured the decision of Lord Sumption (Lords Reed and Briggs concurring on this issue), who concluded that the issue of plausibility is just an aspect of the underlying principle of sufficiency: that a patent monopoly must be justified by the technical contribution to the art. The principle was that: "the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true" and, whilst the common general knowledge may be useful in interpreting the

Patent Litigation

teaching of a patent, there must be a disclosure in the patent to which the common general knowledge is applied. This disclosure cannot be merely that something is worth trying. However, for second medical use claims the disclosure may, for example, amount to reasonable scientific grounds for the skilled person to expect there were reasonable prospects of the invention working based on “a direct effect on a metabolic mechanism specifically involved in the disease”. The test is “relatively undemanding” and is applied to a “modest standard” at the effective date of the patent.

Lords Hodge and Mance dissented, stating their view that the EPO authorities were clear that the standard of proof required for plausibility was lower and satisfied if there was a claim which “appears scientifically possible, even though it cannot be said to be even *prima facie* established, without for example testing or assays”. Their Lordships thought that “only if the person skilled in the art would have significant doubts about the workability of the invention” from the disclosure in the patent would the patent be then implausible.

Infringement

While the Lordships’ comments on this issue are obiter, they make for an interesting read.

In relation to indirect infringement, quite simply, the Supreme Court unanimously agreed that prescribing, dispensing or using generic pregabalin to treat the patented indication does not put the invention into effect, nor does it supply means essential to put the invention into effect. This is because, as explained by Arnold J at first instance, Swiss-type claims protect the manufacture of pregabalin for the designated use and not the subsequent use of pregabalin in treating the patients.

The position on direct infringement is much more complex, with a 2:2:1 split in opinion. Lords Sumption and Reed favoured the “outward presentation” test, in which the intention of the infringer is irrelevant and the sole criteria for determining infringement is how the product is presented post-manufacture (i.e., what is expressly stated in the summary of product characteristics (SmPC) and patient information leaflet). In reaching that conclusion, the Lordships suggested that an infringement test based on intention would be “contrary to principle and productive of arbitrary and absurd results”. While acknowledging that the outward presentation test is not perfect, they nevertheless considered it to be “less imperfect than any other”. Their Lordship appeared to recognise that the proposed test does not address a possible “charade” by a generics company, e.g. labelling its product for one use and actively marketing it for another. However, the patentees’ interest is not the only consideration and this imperfection arose as a direct result of the limitations inherent in Swiss-type claims. It was recognised that “outward presentation” was a rough paraphrase of “*sinnfällige Herrichtung*” or “manifest preparation” which was, until recently, the touchstone of the German courts for the infringement of Swiss-type claims.

Lord Mance proposed a softer version of the outward presentation test, noting that, in rare cases, context may make it obvious that the patient information leaflet and SmPC are not to be taken at face value, and that there may be circumstances where the generic company must positively exclude certain uses. He did not, however, provide any further guidance on what circumstances or context might be relevant. The Judge mentioned the idea of a notice positively excluding the patent-protected use which, according to the authors’ understanding, is not easily done under established principles of regulatory law.

Finally, Lords Hodge and Briggs “not without some reluctance” disagreed with the outward presentation test. They instead favoured a “so-called’ subjective test”, largely supporting Arnold J’s first instance decision. They suggested that whether dealings in the product after manufacture give rise to infringement depends entirely on whether the product was “tainted” during manufacture. They suggested that a mental element in the mind of the manufacturer must form part of a Swiss-type claim (and not s60(1)(c) Patents Act 1977), when the “for” in the patent claim is properly construed. They noted that while the way that the product is presented to the market will “often, or indeed usually” provide evidence of the manufacturer’s intended purposes, the subjective intent may be proved “objectively by words, conduct or even inactivity”, and the Court could rely on “anything from which the court could properly find that the manufacturer had such a purpose could be relied upon, including targeted disclosure, during litigation, of documentary records of the manufacturer’s decision-making process”.

This is a major decision with important ramifications for all stakeholders in the life sciences industry. At first glance, it is perhaps disappointing that the Supreme Court has not chosen to follow the direction of travel in Europe, which is broadly consistent with the approach of the Court of Appeal requiring the generics to take reasonable steps to avoid use of their medicines for the patented indication. However, the fact that the opinion on infringement are: (i) obiter; (ii) specifically restricted to Swiss-type claims; and (iii) leave the door ajar in some respects suggests that this may not be final word on the issue even though it is the end of the road for this case.



CJEU takes a restrictive approach to the grant of SPCs for new formulations of old active ingredients but uncertainty remains



Laura Reynolds
Of Counsel

On 21 March 2019 the CJEU issued its decision in Abraxis¹, which was a reference from the English Patents Court concerning the interpretation of Article 3(d) of the SPC Regulation². Article 3(d) requires that the marketing authorisation ("MA") relied upon as the basis for the SPC is the first MA to place the product on the market in the EEA as a medicinal product. The AG had recommended that the CJEU depart from its previous ruling in Neurim³ and revert to a literal, narrow interpretation of Article 3(d), which the AG considered would be consistent with earlier decisions by the CJEU. The CJEU appears to have taken a literal, narrow approach to Article 3(d) at least in relation to new formulations of old active ingredients but, disappointingly, has not taken the opportunity to clarify how Neurim can be reconciled with the earlier case law or applied in the future.

The SPC application by Abraxis was for its anti-cancer drug Abraxane[®], which contained "nab-paclitaxel" (paclitaxel (an old active ingredient) formulated as albumin bound nanoparticles). Abraxis sought an SPC for the product nab-paclitaxel, which behaves differently to paclitaxel and has enhanced therapeutic properties (but is not for a new therapeutic use). Alternatively, Abraxis sought an SPC for paclitaxel on the basis that the MA for Abraxane was the first relevant MA i.e. the first MA within the scope of the basic patent, relying on the Neurim decision. Paclitaxel had been the subject of several earlier MAs.

Arnold J had upheld the UKIPO's finding that the "product" was paclitaxel (in combination with a substance that was not an active ingredient, namely albumin) ("product" is defined by Article 1(b) as the active ingredient in a medicinal product). This point was not referred. In relation to the application of Neurim, Arnold J considered that, in view of the difficulty in reconciling Neurim with earlier CJEU jurisprudence, the interpretation of Article 3(d) remained unclear and so made a reference to the CJEU. He expressed his opinion that, even though it might sometimes deprive meritorious inventions of SPC protection, it was necessary to have clear rules and Article 3(d) should be interpreted only to permit SPCs for old active ingredients where there was a new therapeutic use.

In the ruling the CJEU re-affirmed the case law that a "carrier" which does not have any therapeutic use of its own cannot be considered a "product". More importantly, the CJEU held that Article 3(d), read in conjunction with Article 1(b), must be interpreted to mean that the MA for a new formulation of an old active ingredient cannot be regarded as the first MA for the product concerned, where that active ingredient has already been the subject of an earlier MA.

Although this appears to give clarity for new formulations of old products, it remains unclear as to how this can be reconciled with Neurim, which was not overturned. In its decision the CJEU merely states that Neurim cannot call the earlier case law into question and quotes the decision in Neurim that "the mere

existence of an earlier MA obtained for a veterinary medicinal product does not preclude the grant of an SPC for a different application of the same product for which an MA has been granted, provided that the application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the SPC application" (emphasis added).

Given that in Neurim the patent claim was for a new formulation of an old active ingredient, the key differences between Neurim and Abraxis seems to have been that in Neurim the earlier MAs were for a veterinary medicinal product and/or for a new therapeutic application. However the CJEU has failed to respond to the AG's request for a clarification as to how Neurim can be reconciled with the earlier case law, in particular:

- a) can an SPC be granted for any new therapeutic application;
- b) can an SPC be granted only where the earlier MAs were for veterinary medicinal products; or
- c) can an SPC only be granted for a new therapeutic application where the earlier MAs were for veterinary medicinal products?

Further, if SPCs are permitted for new therapeutic indications, what about second therapeutic applications, which the AG considered were precluded?

The CJEU cites a number of paragraphs of the AG's opinion with approval, including some of his comments on the situations in which derivatives, such as salts and esters, could be entitled to a separate SPC. However, interestingly, the CJEU does not cite the paragraph of the AG's opinion⁴ where the AG suggested that such SPCs should only be permitted for "new and distinct" active ingredients. In the footnote to this paragraph the AG noted that the conditions under which a derivative could be considered to be a distinct active ingredient had not been addressed by the CJEU and suggested that one approach would be to consider whether it was a new active ingredient within the meaning of the EU rules relating to placing on the market of medicinal products.

No doubt there will be further references both in relation to this and the situations in which Neurim can be applied. As readers may be aware there is already a pending reference (Santen C-673/18) from the Paris Court of Appeal as to the correct interpretation of Article 3(d) in the light of Neurim, which asks, inter alia, whether Neurim is limited to:

- i. cases of human application after veterinary application;
- ii. indications in a new therapeutic field; or
- iii. cases where the active ingredient exerts a different action to that exerted by it in the drug that was subject to the earlier MA.

Overall, Abraxis may be added to the long line of missed opportunities to provide clarity to the interpretation of the SPC Regulation. If any point of principle can be extracted from this decision, it is that the direction of travel continues to be slightly more restrictive.

1 C-443/17

2 No 469/2009

3 C-130/11

4 Paragraph 68 Advocate General (AG) Saugmandsgaard Øe's Opinion of 13 December 2018

Court of Appeal hands down its first ruling on infringement under the doctrine of equivalents



Dr Gregory Bacon
Partner



Manuel Rey-Alvite Villar
Professional Support Lawyer

Last year's Supreme Court judgment in *Actavis*⁵ shook the foundations of modern UK patent law by reintroducing a true form of the doctrine of equivalents. In its recent decision in *Icescape v Ice-World*⁶, the Court of Appeal has seized the opportunity to address some of the many questions raised by this new approach to patent infringement.

For nearly three decades, the English courts had more or less consistently adopted a purposive approach to patent claim construction, an approach encapsulated in Lord Hoffmann's famous "bedrock question" in *Kirin-Amgen*⁷, which required the Judge to shed light on what a person skilled in the art would have understood the patentee to be using the language of the claim to mean, and no more. However, the beauty of this single but complex interpretative test was perhaps lost on the Supreme Court panel in *Actavis*. Lord Neuberger found the approach taken by the bedrock question to be wrong in principle, and sought to better accommodate the mandate of the Protocol on the Interpretation of Article 69 of the European Patent Convention to give due account to equivalents by way of a two-step test. This test required asking: (i) whether the variant infringes any of the claims as a matter of normal interpretation; and (ii) if not, whether the variant nevertheless infringes because it varies from the invention in a way or ways which is or are immaterial. The second limb of the test was to be elucidated by reference to a reformulation of another of Lord Hoffmann's contributions to the law on construction, the so-called Improver questions⁸, which had slowly fallen out of fashion after *Kirin-Amgen*.

As one would expect, the decision in *Actavis* raised as many questions as it answered. Perhaps chief among them was what would in practice be the correct meaning of the term "normal interpretation" in the first limb of the test, and of the term "literal interpretation" in the first of the reformulated Improver questions. The use of these terms by the Supreme Court had practitioners wondering whether purposive construction would continue to play a role in the interpretation of patent claims, or whether we should put it aside and revert to textual infringement to address the first limb of the test. First instance judges such as Arnold J in *Generics (UK) v Yeda Research*⁹ and Henry Carr J in *Illumina v Premaitha*¹⁰ were the first to defend the continued usefulness of purposive construction as a tool for claim construction, Arnold J noting that "I do not consider that Lord Neuberger can have meant anything different, even though he appears to have eschewed the expression 'purposive construction'".¹¹ All eyes were on the Court of Appeal for confirmation that this was the right approach, and that opportunity arose in *Icescape v Ice-World*.

Ice-World's patent concerned ice rink technology. The patent covered a mobile ice rink comprising flexible joints on the pipes carrying the cooling fluid, which enabled the pipes to be folded

up on top of themselves during transportation and then rapidly unfolded to deploy the rink. The system in Claim 1 of the patent had been found to be completely within the common general knowledge save for the use of such flexible joints, which were the core of the invention. However, the claim was framed in such a way that it required the cooling elements of which the rink was comprised to be coupled in a series connection. At first instance, Deputy Judge John Baldwin QC had found that the patent was not entitled to priority and was therefore invalid, but that it would nevertheless not have been infringed by *Icescape's* system. The ruling on priority was upheld by the Court of Appeal, but the issue of infringement remained of importance as it could affect the availability of a defence to a claim of unjustified threats under the old section 70(2A) of the Patents Act (which has since been amended). Although the case had been argued and decided at first instance prior to *Actavis*, the Court of Appeal gave permission to *Ice-World* to advance its infringement case on appeal having regard to equivalents.

Starting with the first limb of the test, Lord Justice Kitchen (as he then was, and in what was one of his last patents decisions in the Court of Appeal following his recent appointment to the Supreme Court) agreed with the approach taken by his colleagues in the Patents Court, and held that he had "no doubt" that Lord Neuberger's reference to "normal interpretation" involved purposive construction.¹² He found that the Deputy Judge had been right to hold that, under a normal, that is to say, purposive, interpretation of Claim 1, *Icescape's* rink did not infringe. A natural reading of the claim, together with the teaching of the specification and the skilled person's common general knowledge, indicated that the cooling elements must be connected in a series, whereas the elements in *Icescape's* system were connected in parallel.

However, this conclusion was no longer the end of the story, as the Court was now required to consider the second limb of the *Actavis* test, namely whether *Icescape's* system would nevertheless infringe because it varied from the invention in ways which were immaterial, an exercise to be conducted in accordance with what Lord Justice Kitchen now called the "*Actavis* questions".

The first of these questions was whether, notwithstanding it was not within the literal (and here Lord Justice Kitchen interpolated "that is to say, normal"¹³) meaning of the claim, *Icescape's* rink achieved substantially the same result in substantially the same way as *Ice-World's* invention, for which the Court must focus on the inventive core of the patent. As set out above, the Court had already determined that the core of *Ice-World's* invention was the use of sufficiently flexible joints so as to facilitate the transportation and deployment of the rink. *Icescape's* rink also achieved this in substantially the same way, answering the first *Actavis* question in the affirmative.

The second *Actavis* question was whether it would be obvious to the skilled person that *Icescape's* rink achieved substantially the same result in substantially the same way as the invention. The Court did not struggle to conclude that this question was also answered in the affirmative, as it would be clear to the skilled person that *Icescape's* rink achieved the same result in precisely the same way.

This left the third *Actavis* question, namely whether the skilled reader of the patent would have concluded that *Ice-World* nonetheless intended that strict compliance with the literal meaning of the claim was an essential element of the invention.

Lord Justice Kitchen once again noted the importance of the inventive core of the patent in addressing this question, and that the fact that the variant is not covered by the language of the claim cannot be sufficient reason to hold that this question is not satisfied. In this case, the inventive core of the patent had nothing to do with whether the coolant fluid flowed through the pipes in series or in parallel, a feature which was found to be inessential, and there was therefore no reason why the skilled reader would have thought that strict compliance with this element of the invention was necessary. The Court therefore overturned the first instance decision on this point, finding that Icescape's rink would have infringed the patent had it been held valid.

Interestingly, since the Court had allowed Ice-World to rely on the doctrine of equivalents, it also allowed Icescape to advance arguments based on the prosecution history, another one of the points considered in *Actavis*. Lord Justice Kitchen however found that Icescape's arguments based on the prosecution history were devoid of merit, and sent a message to practitioners by labelling them "a good illustration of why it is generally so unprofitable to explore the prosecution history"¹⁴.

Many uncertainties remain about the impact of the Supreme Court's decision in *Actavis*, such as the extension of the doctrine of equivalents to immaterial variants that would not have been patentable, or its impact, if any, on the assessment of validity. The Court of Appeal's decision in *Icescape* nevertheless provides welcome clarification on important aspects of the doctrine. It also serves as an illustrative example of a variant that would not have infringed under a purposive construction but will be problematic under the new law, whereby the claims continue to be important, but one must never lose sight of what is wheat and what is chaff.

5 *Actavis v Eli Lilly* [2017] UKSC 48
 6 *Icescape v Ice-World* [2018] EWCA Civ 2219
 7 *Kirin-Amgen v Hoechst Marion Roussel* [2004] UKHL 46
 8 *From the decision of Hoffmann J (as he then was) in Improver v Remington* [1990] FSR 181
 9 *Generics (UK) v Yeda Research* [2017] EWHC 2629 (Pat)
 10 *Illumina v Premaitha* [2017] EWHC 2930 (Pat)
 11 [2017] EWHC 2629 (Pat), at para 138
 12 [2018] EWCA Civ 2219, at para 10
 13 [2018] EWCA Civ 2219, at para 66
 14 [2018] EWCA Civ 2219, at para 79

The short answer is that absolutely nothing of substance happened in 2018. In June 2017 it had come to light that the German President had agreed two months earlier not to sign off on the German legislation which would have enabled his country to ratify the UPC Agreement. This was in response to an action brought in the Constitutional Court, the *Bundesverfassungsgericht* (BVerfG), by a German lawyer called Dr Stjerna. In February 2018 the case was included among those listed for hearing in 2018, but despite the well-deserved German reputation for efficiency, 2018 ended with no sign of a hearing, still less a decision. In fairness, it appears that cases are being heard in the order listed, and the UPC case is now fairly near the top of the list. Hence, we might reasonably expect a decision within a relatively few months. It is also more likely than not that the BVerfG will decide to dismiss the case, thus allowing the President to sign the legislation. However, there is obviously the possibility of an adverse decision, and even if the Court rules in favour of the UPC would Germany actually proceed to ratification? The reason for the doubt is, of course, connected with Brexit.

It had been hoped that the system could start before Brexit so as to avoid arguments about its legality at that stage. Then with the UK a bonafide part of the system, adjustments could be made to address legal issues in advance of Brexit. As it became clear that this would not happen, hope was then pinned on there being a deal with the UK remaining bound for a transition period to EU Regulations including the Unitary Patent Regulation which carries with it the necessity of the UK being a part of the UPC also. In effect, all Member States would have agreed (perhaps unknowingly) to the UK being a part of the UPC during the transition period. Hence if the system could start before 31 December 2020, again issues could be addressed with the UK as a bona fide member of the system. Now as that prospect recedes with the "Mrs May deal" being voted down resoundingly by the UK Parliament, hopes must be pinned on other outcomes. Certainly the project would be more susceptible to legal challenge if there is no deal and the UK is outside the EU at the time of start-up; and it is probably the fear of a legal challenge which is the real problem. Would Germany risk starting a system with a major question mark hanging over its head? It would be a bold step.

What then of other possibilities? Obviously if Brexit were called off, that would solve the problem, but that would be a surprising result in the present political climate with only two major parties in the UK (the SNP and the Liberal Democrats) officially supporting a second referendum which might produce that outcome. Might a deal yet be agreed with a transition period? Possibly, but probably not in the short term. Which leaves the possibility of the Article 50 period being extended. This currently seems the most likely scenario and raises an intriguing possibility for the UPC. If, as has been floated as a possibility, Article 50 were extended to 2020, one could yet see a BVerfG decision in time to allow the UPC to start before Brexit. Perhaps this is now the best chance for the UPC. But as so often before with the UPC, there will surely be more twists and turns in the coming months.

Another year – still no UPC – will 2019 buck the trend?



Alan Johnson
Partner

The highlight of 2018 for the unitary patent and Unified Patent Court project was undoubtedly the ratification of the UPC Agreement by the UK – perhaps not coincidentally on World IP Day last April. It took some by surprise, although quite why is a mystery given the UK's repeated statements that despite Brexit, it still wished to participate in the project. Some simply disbelieved, however, that the UK would actually commit to the UPC by actions and not just words. The significance of UK ratification, of course, is that this leaves only Germany to ratify before the system can come into force. What then of Germany?

Regulatory

Regulatory at Bristows

Our regulatory practice serves the most heavily regulated industries globally, including leading pharmaceutical and biotechnology companies and major manufacturers of medical devices and chemical products. Our team has a wide variety of backgrounds, including the fields of bioscience and genetics with previous experience both in-house and with the UK regulator, the MHRA.

Bristows' life sciences regulatory practice continues to grow

2018 saw enhancement of Bristows' Regulatory practice, with regulatory expert Alex Denoon joining from Marriott Harrison in December to lead the team. Alex, who has more than 20 years' experience advising clients in the Life Sciences sector, joined the firm as a partner and will lead the firm's Life Sciences Regulatory Practice, a team of five experts advising on cutting-edge regulatory issues affecting the biopharma and medical devices industries.

Alex is joined by two new Of Counsel. Julian Hitchcock has focused on the law and regulation of life science technologies since 1997, practising in England and Australia. Julian is a recognised authority on the regulation of regenerative and reproductive medicine, genomics, gene-editing and embryo research, with a particular interest in cell and gene technologies. Julian joined Bristows with Alex in December 2018. Xisca Borrás specialises in all aspects of EU and UK law in the bio-pharmaceutical sector. Previously Xisca was an in-house lawyer at Pfizer, where she provided regulatory law support to all business units and functions at EU and global level, gaining excellent knowledge of the pharmaceutical industry enabling her to bring a strong business approach to her legal advice. Prior to that, she was an Associate in the IP Litigation team at a magic circle law firm in Barcelona for almost 10 years.

The team is completed by associates Eleanor Denny and Zac Fargher. Since joining Bristows, Eleanor has advised clients in relation to regulatory compliance on a broad range of subjects, including on medicinal products, medical devices, cosmetics and food, with a particular focus on pharmaceuticals. Zac was previously a lawyer for the Government Legal Department, advising the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines. In that role, he advised on all aspects of medicines and medical devices regulation and was involved in numerous high profile litigation matters.

The team is also supported by life sciences partner Greg Bacon, who specialises in both IP (patent litigation) and regulatory matters for life sciences clients.

The recent growth of the practice is indicative of the firm's long-term commitment to the Life Sciences sector and its ability to provide a full-service offering to clients in this highly specialised area. Alex commented: "I'm honoured to be at the head of such an experienced and talented group of lawyers, many of whom have industry experience and backgrounds, at one of Europe's leading Life Sciences Practices. The regulatory landscape has never been more challenging for our clients, and we are excited to be dealing with some of the most ground-breaking technologies in the sector."



Left to right:
Greg Bacon, Alex Denoon, Eleanor Denny, Julian Hitchcock, Jack Hostick (Trainee Solicitor), Zac Fargher, Xisca Borrás

Orphan medicinal products: developments in 2018



Xisca Borrás
Of Counsel

Some interesting developments related to orphan biotech medicines took place in 2018. The definition of the concept of “similar medicinal product” was updated in the light of new scientific and technical knowledge in the field of biological medicines, and especially advanced therapy medicinal products (ATMPs). In addition, an interesting decision was issued by the Court of Justice of the European Union related to an orphan medicine produced by recombinant DNA technology in a continuous human cell line.

Introduction

Of the 42 new active substances issued with a marketing authorisation (MA) in the EU in 2018, 17 were orphan medicinal products, doubling the number of orphan medicines authorised in 2017. This suggests that the framework introduced by the Orphan Regulation¹⁵, which lays down the EU procedure for designation of orphan medicines and defines incentives for the development and placing onto the market of designated orphan medicines, is adequate to encourage the development of products to treat rare diseases.

The main incentive of the Orphan Regulation is the 10 year market exclusivity: no regulatory authority in the EU can accept another MA application, or grant an MA, or accept an application to extend an existing MA, for the same therapeutic indication, in respect of a “similar medicinal product” to the orphan medicine, unless the subsequent medicine is safer, more effective or otherwise clinically superior.

“Similar medicinal product”

Commission Regulation (EC) No 847/2000¹⁶ defines the concept of “similar medicinal product” and includes examples of products which are to be regarded as similar for the purposes of the Orphan Regulation. Given that the original definition of “similar medicinal product”, which was more than 15 years old, had proven to be

insufficient for the purposes of assessing similarity for biotech medicinal products, a new definition was introduced in 2018 by way of Regulation (EU) No 2018/781¹⁷. The changes result from the rise of cell therapies and other ATMPs.

Originally “similar medicinal product” meant “a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product and which is intended for the same therapeutic indication”. The original Regulation (EC) No 847/2000 defined “similar active substance” as “an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all the same molecular structural features) and which acts via the same mechanism” and gave examples relevant for biological medicines.

The concept of principal molecular structural features proved unworkable for ATMPs such as cell and gene therapies. Therefore, the definition of “similar active substance” has been expanded for ATMPs to allow similarity to be assessed “on the basis of the biological and functional characteristics”. In addition, the new definition contains examples depending on whether the medicinal products are chemical, biological (other than ATMPs), ATMPs or radiopharmaceuticals which take into account technological progress. Finally, a document with frequently asked questions¹⁸ has been developed with a view to address questions that have been raised by developers of ATMPs regarding the application of the concept of similarity in an ATMP setting. The European Commission will update the document from time to time to reflect new developments.

Shire v EMA (case T-80/16)

In addition to the above, an important decision¹⁹ regarding orphan medicines was issued by the General Court of the Court of Justice of the European Union last year. It is positive for developers of medicines for rare diseases, as it clarifies that a new medicine containing the same active substance as an already approved orphan medicine belonging to the same company group can enjoy its own orphan market exclusivity if the later medicine can show a significant benefit.

The facts of the case

Shire held an MA for the orphan medicinal product Elaprase for the treatment of Hunter syndrome, containing the active substance idursulfase, a copy of the human enzyme iduronate-2-sulfatase, which replaces the enzyme that is missing or defective in patients with Hunter syndrome. Elaprase is produced by recombinant DNA technology in a continuous human cell line and is administered as a concentrate made up into a solution for intravenous infusion (IV). In parallel, Shire developed another medicinal product containing the same idursulfase active substance which could be administered directly into the cerebrospinal fluid intrathecally (IT) to meet an unsatisfied clinical need for treatment of patients with Hunter syndrome, namely those suffering from a severe form of that disease involving cognitive disorders.



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Shire applied for orphan designation for Idursulfase IT for the treatment of cognitive disease in Hunter syndrome patients. The EMA refused to validate Shire's application for the following reasons:

- 1) "cognitive disease in Hunter syndrome patients" was not a distinct medical condition but a severe form of Hunter Syndrome, and
- 2) Idursulfase IT was covered by the Hunter syndrome orphan designation, as the first designation was granted in general terms without specifying a particular form of administration.

Shire challenged the EMA's refusal to validate the application for orphan designation.

Findings of the General Court

The General Court clarified that the mere fact that both Elaprase and Idursulfase IT have the same active substance does not necessarily mean that they are the "same medicinal product", drawing a crucial distinction between the two concepts that the EMA and the European Commission had confused.

Importantly, the General Court ruled that "significant benefit" may be based, amongst other things, on the assumption of a more efficient formulation and means of administration than an authorised medicinal product with the same active substance and intended to treat the same condition. "Particular benefits for a sub-sample of the population" can also provide a significant benefit.

In addition, the decision clarified that an orphan medicinal product can enjoy the period of market exclusivity without precluding a second, similar product from being granted, in turn, market exclusivity, as long as it also fulfils the requirements set out in article 3(1) of the Orphan Regulation. It is equally irrelevant that the MA holder of the original orphan medicinal product and the sponsor of the second product are the same company. The General Court concluded that it cannot be held that the potential designation of Idursulfase IT as an orphan medicinal product, if the relevant conditions are met, would lead, in a future MA, to any "duplication" of market exclusivity or that it would run counter to the objective pursued by the Orphan Regulation.

We are aware that the case has been appealed by the EMA to the European Court of Justice (with case number C-359/18 P)²⁰ but at this time no further information is available regarding progress of the appeal.

Where are we with Brexit?



Dr Gregory Bacon
Partner



Eleanor Denny
Associate

It is clear that the Life Sciences sector is vital to the UK, both with regard to patient health and the British economy. The UK is a global hub for life sciences and in 2017 was noted to have 5,649 life sciences businesses with a presence in the UK that generate a turnover of over £70 bn and employ nearly 241,000 people²¹. However, this sector has developed while the UK was a member of the EU and so the possible implications of, and lack of certainty surrounding, Brexit is causing significant concerns for the industry. As we are getting increasingly close the date scheduled for Brexit, we have set out below a roundup of the key considerations relevant for those working in the life sciences industry from a regulatory perspective.

Background

On 29 March 2017 the UK triggered Article 50 and notified the European Council of its intention to leave the EU. The UK was thus set to leave the EU (i.e. Brexit) on 29 March 2019 and so has had two years to negotiate its withdrawal from the EU or both sides would be left walking into a cliff-edge Brexit in a "no deal" scenario. On 14 November 2018 the UK Government and European Commission (EC) published the finalised Withdrawal Agreement²² (which was an update of the previous Draft Agreement published in March 2018²³) that was agreed at the negotiator level. While the Withdrawal Agreement and the accompanying political declaration were endorsed by the European Council at the meeting on 25 November 2018, the UK Parliament rejected the Withdrawal Agreement by an overwhelming majority on 15 January, 12 March and again on 29 March 2019.

Will very little time before the UK is set to leave the EU under the current Article 50 Notice there is still uncertainty regarding what terms under which it will leave. We have therefore endeavoured to set out below the possible scenarios for those working in the regulatory sector in the UK leading up to 29 March 2019 (now extended to 12 April 2019) and provide some practical suggestions. We will cover: (i) the "no deal" scenario; (ii) the alternative deal/"Plan B" scenario in brief; and (iii) the scenario where Article 50 is withdrawn or the period until the UK exits the EU is extended.

What if there is "no deal"?

As the UK Parliament rejected the Withdrawal Agreement it seems increasingly unlikely that a new deal can be agreed between the UK and the EU before 12 April 2019. Therefore, it is prudent for all those working in the life sciences industry to prepare for a "no deal" Brexit to mitigate the risk of the UK crashing out. Both the UK and EU have produced guidance on this and we have summarised some of the key points below.

The EMA's Questions and Answers regarding the impact of Brexit on centrally approved medicinal products, updated on 1 February 2019²⁴

Those applying for marketing authorisations and/or orphan designations should note that all MA applicants and orphan designation holders must be established in the EU (EEA), and that reference medicinal products for generic, hybrid and biosimilar

15 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, available at <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN>

16 Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority', available at <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:103:0005:0008:en:PDF>

17 Commission Regulation (EU) 2018/781 of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product', available at <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0781&from=EN>

18 Questions and answers related to the assessment of similarity for advanced therapy medicinal products ("ATMPs") in the context of the orphan legislation, available at https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/2018_qa_atmps_en.pdf

19 Judgment of 22 March 2018, Shire Pharmaceuticals Ireland Ltd v EMA, T-80/16, available at <http://curia.europa.eu/juris/document/document.jsf?sessionid=97D73A6AD9EE77497DA44472D21A10797;text=&docid=200546&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=8408886>

20 See publication in the Office Journal at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2018.294.01.0023.02.ENG&toc=OJ.C.2018.294:TOC

applications must be authorised within the EU (EEA). For the purpose of calculating the global marketing authorisation only UK MAs granted pre-Brexit can be considered as the “initial MA”. Also, for prevalence calculations for orphan medicinal products, UK patients will no longer be taken into account post-Brexit within the EU (EEA).

For those with existing MAs or other authorisations/designations, they should be established in the EU (EEA). UK-based organisations holding such authorisations/designations will therefore need to transfer them to an EU (EEA)-based entity. Key personnel (e.g. the Qualified Person for Pharmacovigilance and local representatives), the pharmacovigilance master file and batch control must also be in the EU (EEA), and will need transferring from the UK if appropriate. Additionally, active substances and finished medicinal products manufactured in the UK will be considered as imported products post-Brexit so the necessary import licences into the EU will be required.

Sunset clause provisions require products to be placed on the EU Market so post-Brexit products that have only been placed on the market in the UK will need to also be placed on the market in the Union or their European MA will cease to be valid.

Brexit will also impact on the UK’s competent authorities (CAs) and notified bodies (NBs) as post-Brexit UK CAs will not be CAs for the purpose of EU requirements plus NBs established in the UK cannot act as an applicant for the initial consultation with the EMA for the purpose of medical devices that incorporate medicinal products as an integral part.

The Commission’s Notice to the Product Industry, January 2018 (the Notice)²⁵

Economic Operators: As from the withdrawal date, a manufacturer or importer established in the UK will no longer be considered as an economic operator within the EU. Therefore, distributors in the EU will become importers under Union legislation if they place any products from the UK on the Union market post-withdrawal.

Authorised Representatives/Responsible Persons: Specific legislation requires an authorised representative for certain products (e.g. medical devices) or a responsible person for others (e.g. cosmetic products) to be established in the EU. Therefore, companies may need to move their authorised representative/responsible persons to the EU if they are currently within the UK.

NBs: Under EU product legislation, NBs are required to be established in a Member State and from the withdrawal date, UK NBs will lose their status as EU NBs. It will be necessary for economic operators to take steps to ensure that they will hold certificates issued by a NB in a Member State of the EU, to demonstrate compliance for their products placed on the market as from the withdrawal date. For economic operators who hold certificates issued by a UK NB and plan to continue placing the product on the EU market after Brexit the Notice advises parties to consider either applying for a new certificate issued by an EU NB or to arrange for a transfer.

The UK’s technical notices and “further guidance”

The UK Government has released a series of technical notices and guidance documents that provide guidance for a no-deal Brexit. Three notices of particular importance were: i) how medicines, medical devices and clinical trials would be regulated²⁶; ii) submitting regulatory information on medical products²⁷; and iii) batch testing medicines²⁸, in the event of “no deal”. Additionally, on 3 January 2019 the UK Government published “Further guidance on the regulation of medicines, medical devices and clinical trials

if there’s no Brexit deal”²⁹. The key points of this guidance regarding what will happen after 12 April 2019 from a UK perspective if there is no Brexit deal are summarised below.

Medicines: the UK’s participation in the European regulatory network would stop and so the MHRA would take on the functions carried out by the EU, which would require updates to the Human Medicines Regulations 2012 (the UK legislation). The notices confirm that all centrally authorised medicines will automatically be ‘grandfathered’ into national UK MAs on 12 April 2019; future MA applications will have to be submitted to the MHRA as well as the EMA; the UK MA holder will need to be established in the UK by the end of 2020 (although the further guidance noted those without a presence will have four weeks to nominate a contact person) and certain personnel (the Qualified Person Responsible for Pharmacovigilance (QPPV) and the Qualified Person for manufacture (QP) if the product is manufactured in the UK or a country not on a designated “whitelist”) will need to be established/reside in the UK.

Wholesalers importing QP-certified products from the EU will need to notify the MHRA within 6 months of Brexit to obtain a revised licence and from the date of Brexit will need to establish an assurance system overseen by a “Responsible Person for Import”. Also, parallel imports may continue from the EU post-Brexit under a parallel import licence; however, the MHRA reserves the right “to vary, suspend or revoke a parallel import licence if the UK reference product is suspended, revoked or varied.” Additionally, the further guidance added that the 10 year orphan market exclusivity period will be replicated in the UK.

Medical Devices: while UK presence in any EU committees will cease, the UK will recognise medical devices approved for the EU market and which are CE marked (if this changes the Government promises to give “adequate time” for business to make the necessary changes). The UK will also comply with all “key elements” of the new EU Regulations coming into force, i.e. the Medical Devices Regulation in 2020 and the In Vitro Diagnostic Device Regulation in 2022.

A press release³⁰ in respect of the further guidance indicates that “for a time-limited period, devices that have a CE-mark from a notified body based in the UK or an EU country will continue to be recognised by UK law and allowed to be placed on the UK market” but (in line with the Notice) the MHRA will no longer be able to oversee NBs under the EU regime. Additionally, the UK Government has also confirmed that after Brexit, all medical devices, active implantable medical devices, in vitro diagnostic medical devices and custom-made devices will need to be registered with the MHRA prior to being placed on the UK market. However, grace periods of between 4 and 12 months have been provided, depending on class of device, before registration with the UK is required for products that are already CE marked.

Clinical Trials: The requirements and procedures for clinical trials in the UK are set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 and these will stay in force post-Brexit (subject to some modification to make sure they still work). However, while the new EU Clinical Trials Regulation 536/2014 (CTR) will not apply in the EU on exit day the “Further guidance” reiterated the UK Government’s commitment to align with the parts of the CTR that are in their control.

The further guidance also notes that the UK is seeking to preserve the requirement that the sponsor/ legal representative needs to be based in the EU/EEA but there will likely need to be someone based in the UK with overall responsibility. In addition the UK Government has indicated that it intends to align the UK’s transparency provisions

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with those currently within the EU. Also, as with wholesale dealers, those holding manufacturing licences (MIA) for investigational medicinal products (IMPs) will be required to set up an assurance system to check IMPs have been QP certified in the EU/EEA (although this will be overseen by the QP).

Submitting regulatory information on medicinal products:

If there is a no-deal Brexit the UK would no longer be a part of the EU regulatory networks and so will not have access to their portals (e.g. CESP, the EMA Gateway, EudraCT etc.). Therefore, information required by both UK and EU regulators would have to be submitted twice (onto the existing EU networks and a new national portal run by the MHRA).

Batch testing medicines: Post-Brexit the UK has confirmed that medicines batch tested in countries on an MHRA-approved list (i.e. those in the EU and EEA, and third countries under a mutual recognition agreement) can continue to be supplied into the UK and so the status quo will be maintained. This same approach will apply to Investigational Medicinal Products (IMPs) which are used in clinical trials (save that there are no mutual recognition agreements for IMPs with third countries).

What if another agreement/Plan B is agreed?

Although the Withdrawal Agreement has been rejected three times (to date) by the UK Parliament, it remains the only post-Brexit deal (at present) that the UK Government had been willing to countenance although some movement on the future political declarations (to follow the Withdrawal Agreement) appeared possible at the time of writing. It still seems unlikely that a wholly different agreement or plan B will be implemented in the near future. The Government has also indicated that it may try to put the Withdrawal Agreement to a fourth vote in Parliament. We have therefore summarised some of the key provisions of the Withdrawal Agreement below as they would apply to products in the life sciences sector, in case the Withdrawal Agreement comes to pass and the UK does eventually leave the EU on these terms.

Continued circulation of goods (Article 41): Any individual goods already lawfully placed on either the UK or EU markets before the end of the transition period may continue to be made available and circulate between the two markets until they reach their end-user. However, the Agreement does not make arrangement for goods placed on the market after the transition period ends so significant uncertainty remains about future trade deals.

Market surveillance (Article 43): Market surveillance authorities of the remaining Member States and the UK must without delay exchange relevant information (e.g. regarding goods presenting a serious risk and measures taken against non-compliant goods) regarding goods placed on the market before the end of the transition period. Also, Member States and the UK must pass on any requests to notified bodies in their territories regarding queries about conformity assessments before the end of the transition period.

Transfer of files and documents regarding ongoing procedures (Article 44): Any relevant files/documents relating to any assessments, approvals and authorisations of medicinal products, veterinary medicinal products, biocidal products or plant varieties³¹ that are led by a UK competent authority, e.g. the MHRA, and are ongoing before the entry into force of the Agreement must be transferred by the UK to a designated competent authority of a remaining Member State in relation to the approval/authorisation sought for the EU.

Information on past authorisation procedures (Article 45): The UK will be required to make available the marketing authorisation

application dossiers of medicinal products authorised by the MHRA before the end of the transition period if requested by a remaining Member State or the EMA and if said information is necessary for the assessment of the marketing authorisation³², and vice versa (i.e. the Member States must make such information available to the UK).

Information held by notified bodies (Article 46): The UK must ensure information held by bodies in relation to their activities as notified bodies is made available at the request of the certificate holder to a notified body established in a Member State before the end of the transition period, and vice versa (i.e. a notified body in a Member State must make such information available to a notified body in the UK).

Article 50

Article 50(3)³³ foresees the possibility of extending the two year period prior to Brexit if the European Council and all Member States unanimously agree. If this was agreed to then the UK would have more time to clarify the terms on which it exits the EU, and the current arrangement would continue beyond 29 March 2019. At the time of writing, the EU has agreed to extend the Article 50 term by a minimum of two weeks, i.e. until 12 April 2019. On the other hand, although Article 50 is silent on this, the CJEU has ruled³⁴ that the UK could unilaterally choose to revoke Article 50 so long as a withdrawal agreement has not entered into force nor the period for negotiating the withdrawal has not expired. This would mean the withdrawal procedure would come to an end and the UK would remain a member of the EU. However, there does not (yet) appear to be any political appetite in the UK to revoke its article 50 vote.

Conclusion

After almost two years of negotiating it still remains unclear under what arrangement the UK will leave the EU, if at all. The two sides spent over 18 months negotiating a Withdrawal Agreement to provide a transition period for the UK; however, this was rejected by the UK Parliament and so with very limited time there does not seem to be any clarity. While many in the life sciences sector are lobbying for a scenario where the UK does not leave with no deal, an alternative arrangement may be difficult to achieve in limited time. Therefore, as advised, companies should mitigate their risks by preparing for a no deal Brexit and failure to do so could have disastrous consequences for business continuity within the UK and EU come 30 March 2019. Those who have not started to prepare could have left some things too late so we would recommend contacting your advisers immediately so you can mitigate your risks to the extent possible.

Please note that this is a summary of the regulatory issues and possible scenarios at the time of writing and so the position could still change. Therefore, we recommend contacting your advisors before taking any steps so that you can discuss possible implications for your business.

21 "Strength and Opportunity 2017: the landscape of the medical technology and biopharmaceutical sectors in the UK", https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/707072/strength-and-opportunity-2017-bioscience-technology.pdf

22 https://ec.europa.eu/commission/sites/beta-political/files/draft_withdrawal_agreement_0.pdf

23 https://ec.europa.eu/commission/sites/beta-political/files/draft_agreement_coloured.pdf

24 https://www.ema.europa.eu/documents/other/questions-answers-related-united-kingdoms-withdrawal-european-union-regard-medicinal-products-human_en.pdf

25 https://ec.europa.eu/info/sites/info/files/file_import/industrial_products_en_1.pdf

26 <https://www.gov.uk/government/publications/how-medicines-medical-devices-and-clinical-trials-would-be-regulated-if-there-is-no-brexit-deal>

27 <https://www.gov.uk/government/publications/submitting-regulatory-information-on-medical-products-if-there-is-no-brexit-deal>

28 <https://www.gov.uk/government/publications/submitting-regulatory-information-on-medical-products-if-there-is-no-brexit-deal>

29 <https://www.gov.uk/government/publications/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-there-is-no-brexit-deal/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-there-is-no-brexit-deal>

30 <https://www.gov.uk/government/news/mhra-releases-response-to-consultation-on-eu-exit-no-deal-legislative-proposals>

31 Directive 2001/83/EC; Directive 2001/82/EC; Regulation (EU) No 528/2012; and Regulation (EC) No 1107/2009

32 Under Articles 10 and 10a of Directive 2001/83/EC or Articles 13 and 13a of Directive 2001/82/EC

33 <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A12012M050>

34 <http://curia.europa.eu/juris/document/document>

Keeping Pace: Will the MHRA's no-deal marketing authorisation assessment routes meet their mark?



Alex Denoon
Partner



Zac Fargher
Associate

The looming reality of a no-deal Brexit (at the time of writing this article) throws the UK's responses into sharp relief. In terms of medicines, one of the most interesting proposals is to introduce new assessment routes for UK marketing authorisation applications. The UK will need to attract new medicines to the market – but will these proposals be enough?

Context: marketing authorisations post-Brexit

The Medicines and Healthcare products Regulatory Agency (MHRA) has laid out³⁵ the fate of marketing authorisations (MAs) after a no-deal Brexit.³⁶ The MHRA will continue to respect existing MAs. UK MAs are unaffected while MAs granted by the European Medicines Agency (EMA) will automatically spawn UK MAs.

New MAs granted by the EMA after exit-date will not extend to the UK. Therefore, anyone seeking to sell or supply a new medicinal product in the UK will need to obtain a separate UK MA.

The proposal: truncated timeframes

One of the primary concerns with a no-deal Brexit, in respect of life sciences, is that companies may forgo or delay applications to supply medicines in the UK in favor of the larger EU market, particularly if applying in the UK will duplicate cost and effort. The MHRA response is a streamlined application processes for UK MAs for new active substances and biosimilars. This article focusses on the 'targeted' and 'accelerated' assessment routes:³⁷

- Targeted assessment: where an application is submitted to the EMA and has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) the MHRA will assess the submission within 67 days. There is a presumption that the MHRA will grant an application unless it identifies a public health concern.
- Accelerated assessment: This procedure is a full assessment for new active substances (without the benefit of a CHMP opinion). The timeframe for this procedure has been set as no more than 150 days (a significant reduction from the current 210 day timeframe).

Will these meet their mark?

Targeted and accelerated assessments of new applications is welcome. Businesses undertake comprehensive cost-benefit analyses when determining when and where to make MA applications. Applications for entry into the EU market tend to be prioritised over access to the UK market alone. This is reflected in the number of MAs which are sought in the EU but not in third countries. The Office of Health Economics found that, of

applications made to the EMA during 2013-2015, 45% had not been submitted in each of Australia, Canada and Switzerland by the end of 2016. 15% of these applications were submitted in none of these countries. Of applications that were submitted in the third countries subsequent to the EMA, there was a median delay in submission time of two-three months, and a delay of over one year in 5-15% of cases³⁸.

A number of factors suggest the UK may not experience this trend to the same degree as other third countries: the UK will remain a large market and the MHRA is a respected agency. However, these alone may not be sufficient to insulate the UK altogether. As such, the MHRA must offer further incentives, such as the targeted and accelerated assessments. Even more importantly though, these offers need to be taken up by the industry. To that end, there are a few features of these routes that the MHRA may wish to consider:

- The timeframes must be adhered to: One issue with truncated timeframes as an incentive is compliance. While the MHRA tends to meet its targets for processing new applications³⁹, it will need to retain the resources (particularly staff) to meet tighter timeframes.
- Clarity needs to be provided on 'public health concerns': Applicants need certainty. While Targeted Assessment seeks to provide this, applicants may be concerned as to the MHRA's discretion to depart from a CHMP opinion on public health grounds. This concern was raised by industry⁴⁰, which proposed a standard of "significant public health concern".
- The scope of the routes needs to be extended: There is a real concern that the UK could face medicines shortages. Consequently, the MHRA has indicated that it is considering expanding the accelerated processes for generics, line extensions and new variations.

As with all aspects of Brexit, the future of MA applications in the UK after Brexit will be a matter of 'wait-and-see'.

³⁵ Which are most recently summarised in the MHRA's [Further guidance note on medicines, medical devices and clinical trials](#), 4 January 2019, available online.

³⁶ Scheduled for 212 April 2019 at the time of writing this article.

³⁷ The MHRA is also proposing a 'rolling review' for new active substances, and conditional MA conversions. In addition, the traditional 210 day national licensing route will subsist. However, the MHRA has committed to "identifying options" to reduce this timeframe to a 180 day maximum.

³⁸ These findings were set out in the Office of Health Economics report: Public Health and Economic Implications of the United Kingdom Exiting the EU and the Single Market, November 2017, which was commissioned by the Association of British Pharmaceutical Industry and the BioIndustry Association.

³⁹ <https://www.gov.uk/government/statistics/medicines-licensing-time-based-performance-measures>.

⁴⁰ The Association of the British Pharmaceutical Industry and the UK BioIndustry Association submitted a joint response to the MHRA's contingency legislation consultation process.

2019 looks to be a pivotal and challenging year for the medical devices sector in Europe



Alex Denoon
Partner

The regulatory framework for medical devices is undergoing its most significant regulatory challenge for three decades.

The timeframes for compliance with the new Medical Devices Regulation (MDR) are coming into focus, and the May 2020 deadline looms. In parallel with MDR, all Notified Bodies are applying for their own jobs (applying to be MDR-certified). The challenges facing Notified Bodies have already led to at least one profit warning by a multinational device company. We anticipate further rationalisation of the Notified Bodies, potentially on very short notice.

The regulatory changes and Notified Body issues will affect virtually all players, including third parties such as component and raw materials suppliers, and CMOs. Companies should stress-test their manufacturing and supply chains to endeavour to accommodate disruption wherever possible.

All of this is happening at the same time as the explosive growth in digital health, big data and Artificial Intelligence. By way of example, in January 2019 Novartis' CEO stated that Novartis intends to "Go Big on Data and Digital"⁴¹ and announced a five-year deal with the Big Data Institute in Oxford to use Artificial Intelligence and advanced analytics to improve drug development.

MDR Preparedness

It has been widely reported that BSI (one of the current Notified Bodies) has told its customers:

- to submit any MDD renewal applications (to take advantage of the transition procedures) to BSI by the end of Q1 2019; and
- to expect MDR re-certification to take six to nine months.

This means that any manufacturer seeking:

- to renew an existing certificate to rely on the MDR transitional periods, must finalise its dossier immediately; and
- an MDR certificate from BSI by May 2020 should submit its dossier to BSI before the end of August 2019 or possibly November 2019 (using the more optimistic estimate of 6 months). Novel devices will inevitably take longer.

As a result, we already see clients focusing on their existing portfolios and dedicating significant resources to finalising dossiers for review. Some companies will inevitably miss these deadlines, with significant impact.

The Notified Body Bottleneck

The timetable for MDR compliance is already very challenging and will be under further pressure as a result of the Notified Body re-certification bottleneck.

On 4 December 2018, the Commission published a State-of-Play document (which appeared to have been written in October 2018), which stated that 28 Notified Bodies had applied for MDR certification. This is less than half of the 57 Notified Bodies currently authorised under the MDD. On 19 December 2018, MedTech Europe issued a press release emphasising the need to have Notified Bodies MDR-certified as soon as possible and described this issue as the industry's highest concern.

On 21 January 2019, BSI received the first certificate. This means that sixteen months before the MDR takes effect, one out of 57 Notified Bodies is authorised to issue certificates under the MDR.

We have spoken to numerous people experiencing very significant delays in getting their products approved or renewed. We expect this to get worse before it gets better.

Challenges and Opportunities

Manifestly, 2019 looks likely to be a crucial year for many in the medical devices sector and any issues that arise in 2019 may take years to resolve. Inevitably, these challenges will also generate opportunities and we anticipate a significant amount of M&A activity in the sector in 2019.

⁴¹ <https://www.novartis.com/sites/www.novartis.com/files/2019-novartis-ipmorgan-presentation>.



Are organisms that are the product of mutagenesis subject to the GMO Directive on deliberate release?



Eleanor Denny
Associate

In case C-528/16⁴² proceedings were brought between the French agricultural union and eight associations (the Applicants) against the French Prime Minister and the French Minister for Agriculture, the Food Processing Industry and Forestry (French Ministers) regarding the interpretation of Articles 2 and 3, as well as Annexes IA and IB, of Directive 2001/18/EC (the Directive), which sets out requirements and obligations on those that deliberately release genetically modified organisms (GMOs) into the environment, plus interpretation of Article 4 of Directive 2002/53/EC (as amended). This article focuses on the CJEU's decision regarding whether organisms obtained by mutagenesis are subject to the Directive.

The Directive

The CJEU noted the key provisions from the Directive providing the legal context for this reference:

Recitals

The CJEU referred to Recitals 4-6, 8, 17, 44 and 55 of the Directive. Importantly, the CJEU noted that organisms released into the environment may reproduce and cross national frontiers and the effects of this may be irreversible (Recital 4); the precautionary principle was taken into account when drafting the Directive and must be taken into account when implementing it (Recital 8); the Directive should not apply to organisms obtained through certain techniques of GM that are conventionally used in a number of applications and have a long safety record (Recital 17); and it is important to follow closely the development and use of GMOs (Recital 55).

Articles

Article 2(2) of the Directive sets out the meaning of a GMO⁴³ as an organism whose genetic material has been altered in an unnatural way. It states that "Within the terms of this definition:

- (a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1;
- (b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification" (emphasis added).

Article 3(1) then sets out that the Directive "shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B." Annex IB itself states "Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are: (1) mutagenesis..."

National Arguments

The Applicants submitted that mutagenesis techniques have evolved to produce similar outcomes to transgenesis, e.g. they

can produce herbicide-resistant varieties. Organisms produced by such techniques/ methods were potentially not subject to the obligations of the Directive, even though the Applicants submitted these varieties present risks to health and the environment.

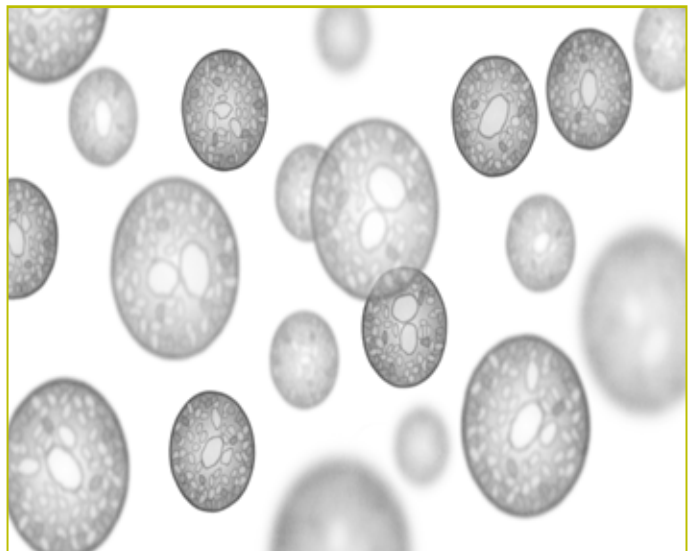
However, the French Ministers argued the application was unfounded as the risks arose from the grower's cultivation practices rather than the GMOs themselves. Also, they argued the new techniques of directed mutagenesis are similar to spontaneous or randomly introduced mutations and unintentional mutations can be eliminated by crossing techniques.

The French court decided to refer to question to the CJEU as, while conventional *in vivo* mutagenesis had been used for decades without identified risks, it was not possible to determine the extent of the risks relating to the new techniques (e.g. random mutagenesis applied *in vitro* to plant cells and directed mutagenesis techniques) and the court thought said risks would be, in part, similar to those of transgenesis. Also the increased rate of mutations from the new techniques led to higher risk.

Decision of the Grand Chamber⁴⁴ of the CJEU

The CJEU had to determine whether Article 2(2) of the Directive means that organisms obtained by techniques/ methods of mutagenesis constitute GMOs and even if so, whether Article 3(1) (read in conjunction with part 1 of Annex IB and recital 17) meant that such organisms are excluded from the scope of the Directive.

The CJEU concluded that Article 2(2) must be interpreted as meaning organisms obtained by mutagenesis constitute GMOs. The Court reasoned that mutations brought about by mutagenesis (in this case intended to produce herbicide-resistant varieties) constitute alterations to the genetic material, and that techniques that involve chemical or physical mutagenesis agents, as well as other techniques that involve genetic engineering, alter genetic material in a way that does not occur naturally. Furthermore, while mutagenesis is not listed in part 1 of Annex IA, this does not exclude it from being a GM technique as part 1 is not an exhaustive list⁴⁵. In addition, mutagenesis is not included in the exhaustive list of techniques not resulting in GMOs in part 2 of Annex IA and mutagenesis is referred to in Annex IB (i.e. the list of techniques/ methods of GM excluded from the Scope of the Directive under Article 3(1)).



Regulatory

The CJEU therefore needed to determine whether GMOs obtained by mutagenesis were excluded from the requirements of the Directive under Article 3(1). The Court stated that while legislation should be interpreted strictly, reading Article 3(1) solely in conjunction with point 1 of Annex IB did not provide conclusive guidance on which techniques should be excluded. It was necessary to consider the context of the wording and the objectives of the rules; the CJEU referred to the recitals (listed above) and importantly recital 17, which sets out when something should be excluded from the scope of the Directive.

The CJEU concluded that Article 3(1) when read with point 1 of Annex IB “cannot be interpreted as excluding... organisms obtained by means of new techniques/methods of mutagenesis which have appeared or have been mostly developed since Directive 2001/18 was adopted. Such an interpretation would fail to have regard to the intention of the EU legislature, reflected in recital 17”. Therefore, “Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 thereof, must be interpreted as meaning that only organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that directive” (emphasis added).

It was then determined by the CJEU that Article 4(4) of Directive 2002/53/EC should be read in light of the above interpretation. Therefore, it “must be interpreted as meaning that genetically modified varieties obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are exempt from the obligations laid down in that provision”; however, other techniques would not be so exempt.

Possible future developments

On 13 November 2018 the Commission’s Chief Scientific Advisors published a statement on the regulation of gene editing⁴⁶ in response to the CJEU’s judgment (the Statement). The Statement discussed the judgment, its implications for GMOs and provided suggestions for regulating them going forwards from a scientific perspective.

Perhaps most importantly the Statement set out that “the GMO Directive [is] no longer fit for purpose” in light of new scientific knowledge and recent technical developments. It noted that hindering EU progress in this field could have a negative impact on research and development and may prevent gene editing techniques from being used, for example, for environmental applications, improving food production/ reducing food scarcity and improving nutritional content. The Advisors also noted this could in turn impact developing countries that may avoid using gene editing techniques if they follow the EU authorisation practices.

The Statement discussed the current definition of a GMO as it relates to an organism that has been altered in a way that has not occurred “naturally”. However, the Advisors noted that mutations occur naturally (i.e. spontaneously/ without human intervention) and can lead to point mutations, insertions, deletions and rearrangements of the genome. Therefore, they advise that the concept “naturalness” should be based on current scientific evidence of what occurs naturally.

The concept of “safety” was discussed at length in the Statement in light of the fact the CJEU’s judgment determined that organisms obtained by techniques without a long safety record should fall within the scope of the Directive. However, the Advisors reasoned that “[i]n scientific terms what is more relevant is, whether or not the products have a long safety record, rather than the techniques used to generate them” (emphasis added). Following the decision it would be possible to have two organisms with the same mutations regulated differently just because they were produced by different techniques on the grounds of safety, which is not entirely aligned with the views of the Advisors.

The Advisors also argued that while the CJEU noted that directed mutagenesis produced new varieties at a higher rate and in larger quantities, this was a less important consideration when determining the safety of a product than control over the mutations that occur. More targeted gene editing techniques were noted to be potentially safer than random techniques as the mutations occur in specific and known locations and should lead to fewer “unintended effects” (i.e. mutations that occur other than those leading to the desired trait(s)). Finally, the Advisors also noted that the impossibility of distinguishing between spontaneously occurring mutations and those created by different types of human interventions was a key issue for the regulatory framework. Therefore, the regulatory framework should put more emphasis on the features of the end product and not the production technique.

Implications

Prior to the decision there had been a question hanging over the interpretation of these provisions for some time leading to uncertainty in the industry as to whether an organism obtained by mutagenesis was always exempt from the Directive or whether there was a requirement to comply with the GMO legislation in some instances. The clarification from the CJEU provides some certainty as to what will be caught by the Directive. However, as recital 55 of Directive 2001/18/EC provides for the legislation to follow the development of GMOs closely it remains to be seen whether over time techniques/ methods currently caught by the CJEU’s interpretation become exempt as they become more widely used and gain a proven safety record.

At present, the Commission has given no indication of an intention to propose updated legislation but, with widespread criticism from those in the industry, it may be difficult for the Commission to delay revisiting the legislation for too long.

⁴² Confédération Paysanne and others

⁴³ “an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.”

⁴⁴ In this case the CJEU sat as the full court, i.e. the Grand Chamber (rather than Chambers of 3-5 judges). This occurs when a Member State or an institution which is a party to the proceedings so requests, and in particularly complex or important cases.

⁴⁵ Part 1 of Annex 1A is a list of techniques/ methods that would constitute GM. It includes the wording “inter alia”, and so is not an exhaustive list.

⁴⁶ https://ec.europa.eu/info/sites/info/files/2018_11_gcsa_statement_gene_editing_2.pdf

Competition

Competition Law at Bristows

Our lawyers are recognised as experts in both national and EU competition law, with a long track record of representing clients before the competition authorities and courts in Brussels, Luxembourg and the UK. Drawing on the firm's wider IP and technical expertise, we advise on everything from current licensing policy through to dealing with competition investigations and the latest changes in competition law.

Small molecule pharma vs biotech: how does EU competition enforcement translate?



Sophie Lawrance
Partner



Aimee Brookes
Associate

Over the last 10-15 years, there has been continuing competition authority interest in the small molecule pharmaceutical sector, with the European Commission and the UK's CMA most recently turning their attention to excessive pricing of generics. Within the past year, the CMA has also been considering discount schemes, as well as a number of other potentially anticompetitive agreements for which details have yet to be released due to the early stage of the investigations. Older decisions in relation 'pay-for-delay' agreements have been making their way through the appeal courts, while follow-on damages claims (brought by purchasing health services) have been making their way through national courts.

How are such regulatory interventions likely to translate into the biotech sector? The key for assessing the applicability of case law based on small molecule medicines to the biotech world is the extent of similarity in the competitive dynamics of each sector.

It is hard to avoid the conclusion that there are some similarities in the competitive dynamics of the two sectors. A key similarity lies arises from patent protection and regulation: both sectors are characterised by a period of product exclusivity, followed by the loss of exclusivity for the manufacturer of the original product. Another factor is regulatory equivalence: both sectors provide for abbreviated regulatory requirements for drugs with the same active ingredient, following loss of exclusivity.

Nevertheless, there are also some important differences, notably the relatively higher cost and complexity of bringing a biosimilar product to market. This greater complexity is well illustrated by the

fact that traditional differences between originators and generic companies (already breaking down in the small molecule sector) scarcely apply – important biosimilar drugs have been brought to market by companies traditionally considered to be originators. Despite the abbreviated regulatory requirements, biosimilars cannot be truly identical to the original product, which results in a somewhat more onerous regime of clinical trials and authorisation, compared to bioequivalent generic drugs.

Given the increasing financial and medical importance of the biotech industry, and the sector already drawing some degree of regulatory attention and analysis of innovation effects and incentives in the merger context (Pfizer/Hospira), we have set out below examples of antitrust issues that have arisen in the small molecule sector which may also have the potential to arise in relation to biotech products. As stated above, there are some differences between these sectors, but experience in the pharmaceutical sector can still provide some useful guidance.

Discounting to capture a larger market share

In December 2015, the CMA opened an investigation into Merck Sharp & Dohme ("MSD") in relation to Remicade (infliximab), one of the first biologic drugs in the EU to face competition from biosimilars. The CMA alleged that, when MSD's Remicade patent expired, it abused its dominant position through the use of a discount scheme to make biosimilar entry more difficult. In particular, the CMA found that "MSD designed its discount scheme in such a way that Biosimilars would have to sell at very low prices in order to compensate the NHS for the discount it would lose on purchases of Remicade if it switched to using Biosimilars for a relatively small proportion of total infliximab demand". That was achieved by requiring the NHS to purchase most of its infliximab requirements from MSD in order to benefit from the discount on purchases of Remicade.

Notwithstanding its preliminary concerns, in March 2019, the CMA issued a decision finding that there were no grounds for action (i.e. no infringement was found). The decision notes the greater complexity and investment required to bring biosimilar products to market, as compared to small molecule generics, but recognises that the competitive dynamics at around the time of entry are fundamentally similar. On the facts, MSD had been largely unsuccessful in producing an exclusionary effect, and had been unlikely to do so in the factual circumstances, as the market worked differently to how MSD had assumed when designing its scheme. The CMA therefore concluded that there was no appreciable harm to competition.

The decision is a reminder that not all discounts granted by dominant companies are contrary to competition law, and a variety of factors need to be assessed before any finding can be made. However, discount schemes can draw the attention of competition authorities when there is a risk that they will foreclose equally efficient competitors, particularly new entrants, such as those with biosimilar products. Even though biosimilar products may represent a relatively lesser cost saving than a generic of a small molecule drug, it is expected that costs will routinely be significantly lower for the later products. Long-term schemes designed to prevent customers from switching to lower-cost biosimilar products may therefore still attract scrutiny, and any anti-competitive effect will be determined on the facts.

Interestingly, the CMA chose a narrow product market definition of Remicade and infliximab biosimilars, in large part because of the

Competition

way the products were administered. A wider definition based on therapeutic substitutability would have included drugs administered at home by patients themselves, but Remicade and infliximab biosimilars were administered intravenously in hospitals. This reflects an increasing trend by competition authorities to define pharmaceutical markets in ways other than by simple reference to the ATC (the WHO's therapeutic index).

Suspensions around safety and efficacy

In the US, Pfizer is calling for FDA guidance on what statements biologic manufacturers are entitled to make about biosimilar products, and has criticised pharma companies for using 'scare tactics' to undermine the adoption of biosimilars. In the EU, a small number of pharmaceutical companies that have been found to have used tactics that cast doubt on the safety and efficacy of a competitor product have come to the attention of regulators.

One case involved an agreement between a licensor and licensee. The agreement between them allowed the licensee to manufacture a product for a different indication from that used by the licensor. Although the licence agreement itself was compliant with competition law, the parties were found to have entered into a subsequent anticompetitive agreement with the purpose of dissemination misleading information that artificially differentiated between those indications. The European Court of Justice held that communications with the regulator and with prescribing professionals must – in line with the companies' regulatory obligations – be presented objectively and without being misleading. Where there was a divergence in scientific opinions, it was incumbent on the product manufacturer to present the available evidence in a balanced manner. The agreement between the parties was considered to amount to a restriction of competition by object, the more serious category of anti-competitive conduct.

This is not the only example of product promotion that has been caught by antitrust rules in the EU. The French competition authority ("FCA") has brought a number of cases against manufacturers accused of denigrating competitors. For example, Sanofi-Aventis was found to have abused its dominant position in relation to Plavix through the use of a marketing campaign that discouraged the prescription of generic alternatives by questioning their safety and efficacy. Sanofi's campaign suggested to medical professionals that they could risk personal liability for any problems that followed the prescription of the generic alternatives.

More recently, the FCA has fined Janssen-Cilag for calling into question the bioequivalence of generic competitors to its Durogesic product (which had been authorised in other EU Member States), and causing a delay to the market entry of the product in France. The case demonstrates the tough line which may be taken on unwarranted regulatory interventions, even if the regulator ultimately reaches a decision which recognises the lack of merit in the arguments raised.

Restrictions placed on availability of reference product

One issue which has emerged in the US (and is now being specifically legislated for in the CREATES Bill – Creating and Restoring Equal Access to Equivalent Samples Act) is the question of access by competitors to supplies of an originator's reference product. Such access is needed in order to carry out the testing required for authorisation. To date, the EU competition authorities have not dealt directly with this issue in case law, perhaps because European regulatory regimes have sufficiently prevented such conduct.

However, if an originator were able to prevent effective access to samples, it cannot be assumed that there would be no competition law consequences. An originator manufacturer may well be dominant, and thus be subject to the 'special responsibility' under Article 102 not to distort competition. One example of such conduct is refusal to deal / supply. Refusing to provide a reference product to a competitor does not fall easily within existing categories of case law. Indeed, there is usually no obligation to deal with non-customer third parties, save in exceptional circumstances where the emergence of a new product for which there is consumer demand is prevented. It is a matter for debate whether a generic or biosimilar product would be regarded as "new" compared to the originator product, although the fact that biosimilar products are not bioequivalent in the manner of generic products may mean that the risk is somewhat greater in that case. However, Article 102 is a flexible instrument and it cannot be excluded that restricting supply of a reference product would be viewed as forming part of the 'tool-box' of conduct designed to prevent competitive entry, as described in the Commission's Pharmaceutical Sector Inquiry final report.

The 2005 Commission Decision in relation to conduct by AstraZeneca ("AZ") (which was subsequently upheld by both the General Court and European Court of Justice) is an example of that flexibility, and has some relevance to the conduct under consideration. In that case, one of the two abuses identified by the Commission was AZ's misuse of regulatory procedures through the selective withdrawal of certain marketing authorisations which could have been relied on by new entrants for satisfying pharmacological and toxicological tests, and clinical trials. Whilst changes to the regulatory system mean this abuse is no longer possible, the decision is a good indication of the likely approach of the European competition authorities to conduct of the type described above.

Extending patent protection

The CJEU has recognised that it is legitimate for pharmaceutical originators to take reasonable steps as a way to minimise the erosion of sales which typically occurs following generic entry. However, where companies hold a dominant position (which on current law should be assumed for most original products prior to effective generic entry) such strategies must be consistent with the company's special responsibility not to distort competition. A number of cases have identified conduct which goes beyond what is considered to be competition on the merits.

The other aspect of the AstraZeneca case was one such example. In the EU, patent holders can obtain Supplementary Protection Certificates ("SPCs") to extend patent protection for five years. However, AZ was found to have infringed competition law by providing misleading information when seeking SPCs for Losec. The extra protection was granted, the entry of cheaper generics was delayed, and competitors had to bring litigation to invalidate the SPCs. AZ also invoked the SPCs to bring patent infringement proceedings against generics. The Commission found that this behaviour constituted an abuse of a dominant position.

The relevance of SPCs in preventing generic products from being prepared for market is still recognised as an important policy issue. One element of the current Commission consultation on the use of SPCs is a proposed waiver to speed up generic entry by allowing preparatory development while an SPC of the reference medicine is still in force.

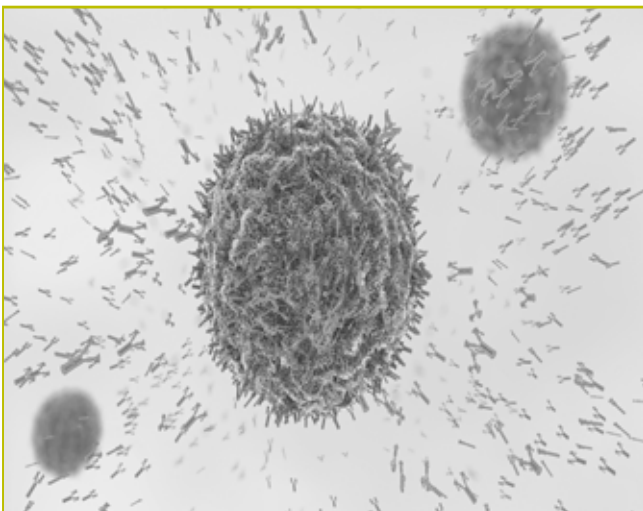
The UK's CMA has also identified 'product hopping' (changing the formulation or dosage of a marketed drug) as an abuse of dominance where it results in significant impediments to generic entry. Reckitt Benckiser removed its original Gaviscon product from the market in favour of a reformulated version, in the knowledge or expectation that this would prevent UK doctors from prescribing a generic version of that original product. Generics could not be substituted for the new product, which was still protected by formulation patents.

Pay for delay

Following its pharmaceutical sector inquiry, completed in 2009, the Commission has focused on patent settlement agreements which featured a value transfer from the IPR holder and restrictions which keep a generic product off the market. Although not every agreement with a value transfer is anticompetitive, the Commission has found that both financial and non-financial benefits may induce generic competitors from seeking to compete on the market. The Commission considers the ultimate outcome of the settled litigation to be of limited importance: such agreements transform an uncertain litigation outcome into the certainty that generic competitors would not enter the market.

In 2013, it issued a decision against Lundbeck and several generic companies in relation to citalopram, and in 2014, it issued a decision against Servier and five generic companies in relation to perindopril. The Commission has found that such settlement agreements are comparable in seriousness to market sharing / exclusion agreements, and to date, the General Court has upheld the Commission's finding in Lundbeck, although a further appeal is still pending before the CJEU, and Servier is awaiting judgment from the General Court in its appeal.

The CMA has also issued a pay for delay decision, against GSK and a number of generic manufacturers in relation to paroxetine. Early last year, the companies appealed the decision to the CAT, and the CAT elected to refer five issues to the CJEU for a preliminary ruling before making a final judgment on the appeal. The CJEU has yet to consider the issues, but any ruling will likely be important guidance on the circumstances in which a settlement agreement will constitute an abuse. Although many biotech settlement agreements will not fall within the scope of the Commission's annual monitoring surveys, as they are not entered into between an originator and a generic company, such guidance is likely to be equally applicable for the biotech sector.



Real Estate

Real Estate at Bristows

Our real estate lawyers offer a comprehensive commercial property service for clients investing in, developing or financing real estate, as well as owners and occupiers of business space. Clients come to us for advice on everything from buying, selling, leasing and managing real estate through to the structuring and establishment of joint ventures and co-investment vehicles, including the launch of new property funds.

Brexit is not Frustrating



Teresa Edmund
Partner



Sukanya Majumdar
Trainee

On 20 February 2019 the High Court ruled against the European Medicines Agency (EMA) in a case brought by its UK landlord, Canary Wharf Group (CWG), which considered whether the UK's withdrawal from the EU enabled the EMA to treat its lease as at an end.

The EMA is the arm of the European Union (EU) responsible for the evaluation, authorisation and monitoring of medicines across the single market. It has been based in London since it was set up in 1995 and, in 2014, it entered into a 25-year lease of a new building at 25-30 Churchill Place at a starting rent of £13m pa. The lease was entered into pursuant to an agreement concluded in 2011 which enabled EMA to input significantly into the building's design.

Following the UK's vote to leave the EU, the EU prescribed⁴⁷ that the EMA should be headquartered in Amsterdam but, unlike the European Banking Authority (which is relocating post-Brexit), the EMA does not have the benefit of a break right in its lease. To avoid paying rent in London until 2039 despite not occupying its offices here, the EMA sought to argue that its lease will be frustrated by Brexit. In addition, it proposed a self-standing argument that by virtue of EU law the EMA had no power to discharge its future obligations under the lease and, as such, the UK is required to provide a remedy for it, even if outside the doctrine of frustration.

Frustration is an exception to the general rule that contracts are an absolute and binding commitment between the parties and can only arise where an event occurs after the contract has been entered into which makes the contract either impossible of performance or radically changes the nature of the obligations under it.

The EMA argued that it could not operate its EU regulatory role from a non-EU country, and being tied to its lease in the UK would

push it beyond powers conferred on it as an EU regulatory body, making discharge of its contractual obligations illegal. The court found that the EMA had proper capacity to enter into the lease in 2014 when it acquired the property, and, regardless of Brexit, there was no doubt that the EMA will continue to have capacity to deal with property which it already holds, even if it is located in a non-EU country. The EMA's argument that the lease will be frustrated as a result of a supervening illegality was therefore rejected by the Court.

The Court also rejected the EMA's argument that the impact of Brexit significantly changes its obligations because it will lose the benefit of a number of protections against contractual liability afforded to it, particularly under Protocol 7⁴⁸. The Court found that, although this protection will be subject to changes by the UK government, the protection is only diminished and not eliminated altogether. The diminished protection in relation to contractual liability will not change the EMA's capacity to perform its contractual obligations under the lease.

The EMA also argued that both it and CWG expected the premises to be used for, and it was designed as, the EMA's headquarters, reflected in the bespoke terms of the lease and the EMA's substantial control over elements of design. In response, the Court emphasised that the parties had divergent commercial purposes, and found that there was no common purpose that the premises be only the EMA's headquarters. Instead, the incorporation of alienation provisions, allowing the EMA to assign the lease, was taken as express agreement between the parties that the lease would continue even if the EMA were not occupying the premises as its headquarters. The alienation provisions, though onerous, were evidence that the EMA had agreed to this possibility, so the argument that its relocation deprived the EMA of any benefit of the lease or frustrated a common purpose was not tenable.

The Court also considered the foreseeability of Brexit at the time the agreement for lease was entered into in 2011, concluding that it was then only a theoretical possibility rather than foreseeable. Despite this, it was foreseeable to the EMA that over the long duration of the lease circumstances might arise which could require the EMA to relocate. Even if Brexit itself was not foreseeable, some change over this length of time was. Again, the alienation provisions affirmed that the EMA had accepted the possibility of such change before entering into the lease, so it could not prove that Brexit will radically change its contractual obligations.

The Court acknowledged the practical, political and economic issues at play in the case. However, it could not find any legal basis for holding that the lease will be frustrated either as a result of supervening illegality or frustration of a common purpose. The EMA's self-standing argument was also rejected, as the court emphasised that the lease is governed by English law only and a remedy beyond frustration could not be justified for the EMA on the sole basis that it is an EU agent.

The case re-enforces judicial reluctance to apply the doctrine of frustration to contracts and leases in particular. To the relief of landlords and other contracting parties, the decision does not assist a party looking to avoid its contractual liabilities as a result of Brexit.

⁴⁷ Regulation (EU) 2018/1718

⁴⁸ Treaty on the European Union and the Treaty on the Functioning of the European Union.

Data Protection

Data Protection at Bristows

With one of the largest teams of data protection lawyers in Europe, we have acted on many of the highest profile and most complex projects of recent years, several of which have made the headlines in the national and international press. This has enabled us to build close working relationships with EU data protection authorities as we deal with them regularly in relation to both advisory and litigious matters.

The OCR press release at the time stated that “in addition to the impermissible disclosure of ePHI, OCR’s investigation revealed that Anthem failed to conduct an enterprise-wide risk analysis, had insufficient procedures to regularly review information system activity, failed to identify and respond to suspected or known security incidents, and failed to implement adequate minimum access controls to prevent the cyber-attackers from accessing sensitive ePHI, beginning as early as February 18, 2014.”

The European Data Protection Supervisor (EDPS) recently published a summary of outcomes from its public consultation on digital ethics and the topic was also discussed at length at the 2018 International Conference of Data Protection and Privacy Commissioners.

The EDPS publication indicated that more than 80% of respondents to their survey affirmed that ethics relating to new technologies is, or will soon be, on the agenda of their organisation, many of them considering it “important”, “extremely relevant”, or even “mandatory” and “a priority”.

Many of the respondents to the survey acknowledged that ethics is more than a tick box exercise and goes beyond merely complying with the law and that “failing in the transparent and fair processing of data can have disruptive effects on the business”.

The Gartner report says that, “any discussion on privacy must be grounded in the broader topic of digital ethics and the trust of your customers, constituents and employees. While privacy and security are foundational components in building trust, trust is actually more than just these components. Trust is the acceptance of the truth of a statement without evidence or investigation. Ultimately an organisation’s position on privacy must be driven by its broader position on ethics and trust. Shifting from privacy to ethics moves the conversation beyond, “are we compliant” toward “are we doing the right thing”.

Even if Scott McNealy was right in 1999 (when he reportedly said, “You have zero privacy anyway – Get over it.”), individuals deserve respect for their privacy. This respect does not always have to be imposed by law, but should be a matter of integrity and ethics.

Ethics and Data Privacy



Robert Bond
Partner

Whilst there has been much attention to data protection as a result of the EU General Data Protection Regulation as well as the recent flurry of similar legislation in other parts of the world including California, Brazil, Bahrain, Kenya and South Africa, the focus for the most part has been on compliance with law and regulation.

Ethics has been a central issue for the Biotech sector for a while but the increasing use of technology, particularly gene technology, raises concerns about not only compliance with law and professional standards, but also ethics and personal data.

Recently the well-known analyst Gartner named digital ethics and privacy as one of Gartner’s top 10 strategic technology trends for 2019. In addition the UK Department for Media, Culture and Sport updated the Data Ethics Framework aimed at public sector saying, “Ethics and innovation are not mutually exclusive. Thinking carefully about how we use our data can help us be better at innovating when we use it.”

As businesses become more used to concepts such as Privacy by Design and make effective use of Privacy Impact Assessments so the notion that, “just because we can, doesn’t always mean we should” is becoming a norm.

The recent flurry of well publicised data breaches and fines are having an impact on those organisations as regards damage to their brand and their position of trust in the eyes of both shareholders and consumers. In October 2018, Anthem, Inc. agreed to pay \$16 million to the U.S. Department of Health and Human Services Office for Civil Rights (OCR) and take substantial corrective action to settle potential violations of the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules after a series of cyberattacks led to the largest health data breach in history and exposed the electronic protected health information of almost 79 million people.

Commercial IP

Commercial IP at Bristows

Consistently ranked among the world's top IP firms, Bristows has a wealth of experience in handling a wide range of deals involving intellectual property rights. Our clients range from multinational household names to small startups, and they seek our advice on protecting and extracting value from their most valuable assets – their inventions and ideas, their brands, their reputation, their secrets and their designs.

BREXIT: Impact on Horizon 2020 and its successor Horizon Europe



Ellen Lambrix
Senior Associate

The UK is a global leader in life sciences with a long history of collaboration between UK research organisations and EU partners. Horizon 2020, the EU's current flagship research programme has played a key role in supporting these collaborations and funding valuable research and innovation in the UK. This article looks at the impact that Brexit will have on the availability of funding for UK based organisations under Horizon 2020 and its successor Horizon Europe.

Horizon 2020 is the EU's current flagship research programme and is the biggest EU research and innovation programme ever with a budget of almost €77 billion. It will be succeeded in 2021 by Horizon Europe which has a proposed budget of €100 billion for 2021-2027.

UK researchers have historically received a disproportionate share of funding under the Horizon 2020 programme compared to their EU counterparts. Figures published by the European Commission show that in the first three years of the Horizon 2020 programme UK researchers and innovators received 15.2% of the overall funding available (second only to Germany) and that UK universities, SMEs and other organisations participated in more EU funded research and innovations projects than their counterparts from any other countries. In addition to providing a key source of funding for UK researchers and innovators, access to Horizon 2020 also facilitates cross border collaborations and strengthens scientific cooperation between companies, universities and other organisations, helping to accelerate medical research and innovation in the UK and EU.

Horizon 2020

Following the UK's 2016 referendum decision to leave the EU, there has been uncertainty regarding the ability of UK companies and research institutions to continue to receive Horizon 2020 funding and to continue to participate in Horizon 2020 projects. At the time of writing of this article, the UK Government and EU had agreed a withdrawal agreement at negotiator level setting out the terms of the UK's exit from the EU but this agreement was overwhelming rejected by the UK Parliament in January 2019 and March 2019. There therefore remains uncertainty as to how UK organisations will continue to be able to participate in Horizon 2020 following the UK's exit from the EU, particularly as the European Commission has made clear that in a 'no deal' scenario, British applicants will cease to be eligible to receive EU funding.

The aspects of the withdrawal agreement that relate to the UK's participation in Horizon 2020 mean (assuming that the withdrawal agreement forms the basis of any future deal) that the UK can to continue to participate in Horizon 2020 until its closure. In particular it has been agreed that existing projects will continue to receive an uninterrupted flow of EU funding for the lifetime of the project and that UK participants will be eligible to bid for Horizon 2020 funding for the duration of the programme.

To address the uncertainty of a 'no deal' scenario and recognising the importance of continued access to Horizon 2020 for UK research and innovation, the UK Government announced in August 2016 that it would underwrite all Horizon 2020 grants for all successful bids for Horizon 2020 funding submitted before the UK exits the EU, for the lifetime of the projects. To help administer the underwrite guarantee the UK Government has invited all UK recipients of Horizon 2020 funding to register their details on a dedicated portal. Building on this, in July 2018 the UK Government announced that it would extend the underwrite guarantee to cover UK participants' funding in all Horizon 2020 requests open to third country participants from the date of exit. The guarantee would cover the lifetime of the projects, even if they last beyond 2020. This was confirmed in the UK Government's technical notice regarding Horizon 2020 funding in a no-deal scenario, published on 23 August 2018 and in an overview paper published on 27 September 2018 which sets out further detail regarding the underwrite guarantee and the post-EU exit guarantee extension. It is important to note that the guarantee only covers funding for UK participants. Concerns have been raised about projects under which a UK organisation is the project coordinator and responsible for distributing funds to EU based partners. The UK guarantee would not cover funding for the relevant EU institutions and in a no-deal scenario the UK coordinator would not be eligible to receive funds from the European Commission (even if earmarked for EU participants). It is not yet clear how this will be addressed and the UK Government had stated that it was seeking to discuss how this could best be addressed in a 'no deal' scenario with the European Commission.

While there are a number of details that would still need to be agreed regarding the UK's participation as a third country, the extension of the underwrite guarantee comes as welcome news to the UK research community who can now look beyond 12 April 2019 and plan research projects with certainty whether or not a deal is reached between the UK and the EU.

Horizon Europe and beyond

Plans for Horizon Europe, the successor to Horizon 2020, are currently under development with the European Commission announcing a proposed budget for the programme of €100 billion for 2021-2027. The UK Government has expressed its commitment to ongoing collaboration in research and innovation and proposed in its white paper published in July 2018 forming a cooperative accord with the EU on science and innovation. In particular the UK has confirmed that it wants to explore association with Horizon Europe which would involve a UK financial contribution. The proposed budget for Horizon Europe currently assumes no contributions or involvement from the UK, however the plans unveiled by the Commission have the potential to significantly broaden international access to the programme, allowing other non-EU “third countries” who meet certain criteria to participate and it is possible that the UK could participate on that basis. In order to achieve this however the UK would need to enter into an agreement with the EU setting out the terms of the UK’s participation. The proposed regulation requires that this agreement must ensure “a fair balance as regards the contributions and benefits” of the UK’s participation and it also makes clear that the UK would not have a “decisional power” on the programme. This means it may not be possible for the UK to achieve the degree of influence over the programme that the UK Government is hoping for. The proposals and budget for Horizon Europe are now being examined and further developed by the European Parliament and Council and discussions regarding the UK’s participation will need to take place between the UK and EU.



Beyond Horizon 2020 and Horizon Europe, the UK Government has also confirmed that it is developing a new international research and innovation strategy which will set out its desire to build on the UK’s long tradition of international collaborations in research and innovation and openness to international talent. In line with this and despite its many difficulties, the UK’s exit from the EU may present an opportunity for the UK to foster increased international collaboration and as an opportunity for UK based companies and researchers to attract more international sources of funding.

Conclusion

Although there remains some uncertainty regarding access to Horizon 2020 funding following the UK’s exit from the EU, the solutions proposed for both a deal and a no deal scenario go a long way to ensure that UK participation in Horizon 2020 funded projects can continue, either in accordance with an agreed withdrawal agreement or underwritten with funding from the UK Government. The UK’s commitment to science and innovation together with continued support for collaborations, both European and international, will be key to ensuring that the UK remains a global leader in life sciences.

CAR-T

Bristows hosts CAR-T event



Laura Anderson
Partner



Rachel Mumby
Senior Associate

In October 2018, only weeks after the first two CAR-T therapies were authorised in the EU, and days after NICE had given the go-ahead for Yescarta and Kymriah to be brought to market for certain types of patient, Bristows hosted a roundtable event to discuss recent developments in the field of CAR-T and other cellular immunotherapies. The attendees all provided different perspectives and enabled an engaging debate to take place. Topics covered included funding and collaboration (from the perspective of universities and commercial bodies), patent and licensing considerations (from an in-house and private practice perspective), manufacturing challenges and also market access issues. Some highlights of the discussion are set out below.

Collaboration between academia and the pharmaceutical industry

The first area for discussion was the great success that has been achieved in this area through close relationships between academia and the pharmaceutical industry. In particular, the traditional business model, where the pharmaceutical industry has worked alone, or just been passed academic work has not been replicated in this area.

It was agreed that the real driver for a change in approach was the incredible efficacy shown in early CAR-T trials. This efficacy meant that some within the pharmaceutical industry were willing to take a risk and invest, even though results had only been seen in tiny numbers of patients. This investment therefore came at a time when ordinarily, only government funding bodies such as the Medical Research Council, or venture capitalists, would get involved. However, the highly experimental nature of this early work still required a flexibility in approach which is only really possible in the academic environment. This meant that the research needed to stay in academia for a while longer, despite the involvement of the pharmaceutical industry. This willingness to invest in what was essentially very early stage research was therefore game changing in terms of the dynamics. It has resulted in both sides being willing to consider more flexible ways of doing business with each other.

On a practical level, universities have also historically not been well placed to execute clinical trials for more traditional small molecule therapies, especially where very large patient cohorts are required. In contrast, academics working in relation to this type of advanced therapy often have clinics at major hospitals and have been able to take therapies they have been developing into the clinic and sometimes all the way through to phase III studies. Universities are also developing their own innovation networks which not only enable the pre-clinical and clinical research but also include

manufacturing sites which are licensed in accordance with current good manufacturing processes (GMP).

Examples of successful tie-ups in this area include Novartis and the University of Pennsylvania, Juno (now part of Celgene) and the Memorial Sloan Kettering Cancer Institute, and Kite (now part of Gilead) and the National Institutes of Health.

Collaboration in manufacturing and the supply chain

Manufacturing and supply chain issues in relation to CAR-T therapies are completely different from those required for traditional small molecule therapies, such as tablets or capsules. Quite apart from the equipment required to process a patient's cells, for CAR-T therapies every step of the process is subject to a strict timetable. This means that everything is coordinated – clinicians will know exactly when they must take cells from the patient such that they can be frozen and shipped to the production facility (which may not be in the same country) to arrive in time to be processed during a pre-booked slot, be subjected to lengthy quality control processes, before being re-frozen and shipped back to the patient.

The group discussed the high demand for university-run GMP manufacturing facilities, and also other facilities such as the Cell and Gene Therapy Catapult facility in Stevenage. This facility can be used by early stage researchers who would not otherwise have access to the necessary infrastructure, or know-how, but who want to join a collaborative environment, where they can continue to develop their therapy themselves rather than signing it over to someone else to undergo this stage of development. The group discussed that without the availability of such specialist facilities and infrastructure, it would be very difficult for start-ups and academic spin-outs to get started and to get the data they need to obtain further funding.

Getting the therapies to market

The game-changing nature of these therapies has meant that not only the scientists, but also regulatory authorities and payers, have had to rethink some of their models as there was no industry standard to follow (and this is still ongoing). It was discussed that companies such as Novartis and Kite are in a situation where they are seeking approval, and more particularly reimbursement, when there is very little efficacy data available (albeit that that data is very strong). The economics of these therapies are also clearly unusual – how do you put a price on a cure, but also how do you assess whether something is a cure, and what happens if there is a relapse in ten years' time?

The role of IP in this area

Traditionally, patents which cover major pharmaceutical therapies still have significant value right until the expiry of those patents, including any term extensions. Such patents are often only asserted in the last few years of their lifetime – this to prevent generic versions of those medicines being sold before the twenty year (or longer) period has expired. However, the group discussed that the same model may not be followed in the CAR-T field, meaning that IP protection may be used quite differently from traditional models and provide value to patentees in different ways. It was noted that whilst at the moment there are only two approved

therapies, these will not remain the only two, and in the next few years there could well be many follow-on therapies. This means that it is unlikely that anyone will be interested in copying Yescarta and Kymriah in 10 or 15 years' time when the IP specifically relating to those products might expire. Instead, the value is more immediate as so many companies are competing in the same space, with the potential for complex cross-licensing. Although this in itself has significant implications for the cost of the therapies if royalty stacks become too onerous.

Another challenge relating to IP in this area, on a purely practical level, is that if company A thinks that company B is infringing its patent, it cannot just obtain the relevant tablets from a pharmacy and analyse them. It is much more difficult for the different players to assess what their competitors are actually doing. In addition there are ethical considerations – these are life-saving medicines which are used when other therapies have failed – are companies going to be willing to start litigation in such circumstances and seek an injunction? Further, where much of the work is done in hospital and university settings, the group could foresee that arguments would be made about whether research or pharmaceutical preparation exemptions apply. The multi-jurisdictional supply chains, often with many entities involved, could also make analysing infringement difficult, especially where patent protection may be different in different jurisdictions.

The future

When many of the participants in the roundtable were at university, this type of therapy was seen as science fiction, but now we are on the cusp of a revolution with cell therapies being commercially available. In the immediate future, seeing the first allogenic therapies come to market will also be fascinating, but all stakeholders, from academics, funding bodies, pharmaceutical companies to payers will need to continue to be flexible and adapt. All in all it is immensely exciting.

Bringing CAR-T to market



Rachel Mumby
Senior Associate

In August 2018, almost exactly one year on from the FDA's first authorisation of a chimeric antigen receptor T cell (CAR-T) therapy, two CAR-T therapies were authorised for use in the European Union. These are Kymriah (which had been developed by Novartis in collaboration with the University of Pennsylvania amongst others) and Yescarta (which had been developed by Kite in collaboration with the National Cancer Institute of the US National Institutes of Health, and is now part of Gilead). The next step for both companies was then to agree on the pricing and reimbursement of these treatments across Europe, as well as ensuring that the necessary infrastructure is in place and training/accreditation completed to enable these therapies to be used.

In the UK, as is typical with new cancer therapies, NICE had begun evaluating both therapies several months earlier. In April 2018, Simon Stevens, the chief executive of NHS England, announced in a speech to the Association of the British Pharmaceutical Industry that preparations were underway to assess making CAR-T therapies available on the NHS. Stevens then indicated that the pharmaceutical industry would have to

work with the NHS, saying "in order for [the therapies] to become widely available, manufacturers need to set fair prices so that they are both affordable and sustainable in the long term".

In fact, preparation had begun at NICE much earlier than that – it published a report on the assessment and appraisal of regenerative medicines and cell therapy products, which had included a mock assessment of a CAR-T therapy, in March 2016. In this report it was noted that these types of technologies present special difficulties for NICE's technology appraisal because they can be expensive per patient and supported by only small-scale single arm studies, but potentially confer substantial health gains. One of the findings of the underlying studies run by the University of York was that in addition to discounting, innovative outcome-based payment methodologies needed to be developed. One suggestion was the use of "lifetime leasing" whereby a monthly fee is paid for the duration of treatment benefits (until death). Another option considered was a variant of that which is now in place in the US for Kymriah. Under the US system, Novartis only gets paid if the patient treated with Kymriah through Medicare or Medicaid responds in the first month of treatment. The option considered by NICE in its mock assessment was that payment should only be made for patients in remission.

NICE's initial analysis of Kymriah and Yescarta was made public shortly after the marketing authorisations were approved. However, the results of this analysis were mixed. For both therapies, NICE had published draft guidance stating that the cost per patient was currently too high for them to be considered a cost-effective use of NHS resources. In coming to this conclusion, it does not appear that the innovative payment methodologies considered under the 2016 mock assessment were considered.

Despite the draft NICE guidance, on Wednesday 5 September 2018, fewer than 10 days after authorisation in the EU, NHS England and Novartis announced that they had reached an agreement in relation to the use of Kymriah in paediatric and young patients (a subset of the approved uses, i.e. not in adults, and not the subject of the NICE draft guidelines). This was made possible by NICE agreeing that funding could be used from the Cancer Drugs Fund for this indication. Similarly, on 5 October 2018, the NHS and Gilead announced that they had reached agreement in relation to the use of Yescarta, whereby up to 200 adult patients a year will receive treatment under the Cancer Drugs Fund (this was after negotiation following NICE earlier deciding that Yescarta did not meet the necessary hurdle for funding from the Cancer Drugs Fund of having the "plausible potential" to be cost effective). In January 2019, Great Ormond Street Hospital announced the first NHS patient to receive CAR-T treatment (Kymriah).

NICE has opened consultations for both therapies with final publication of the NICE guidance taking place in January 2019 for Yescarta and March 2019 (expected) for Kymriah. In the former, NICE recommended use of Yescarta within the Cancer Drugs Fund across its approved indications subject to an agreed patient access scheme, and we await with interest the outcome of the NICE consultation for Kymriah. However, it is impressive that the NHS, in collaboration with Novartis and Kite, has acted so quickly to bring such innovative medicines to patients.

Tax

Tax at Bristows

Our tax experts offer advice on the full range of tax issues affecting corporates, from large multi-nationals to smaller growing companies. Core areas of expertise include helping clients, both UK based and overseas, to structure corporate and commercial transactions, navigating the corporation tax, VAT, stamp duty and employment taxes minefield and making the most of available reliefs and incentives.

Recent Tax Developments



Miranda Cass
Partner



Julia Cockroft
Senior Associate

Overview

The Budget from October 2018 was short on 'headline grabbers' for the life sciences sector which was slightly overshadowed by a focus on conventional technology businesses. However, beyond the front page, there were a number of measures which will have an impact on the biotech industry.

Biotech funding

Start-up and early stage biotech companies will welcome the Treasury's recent response to a consultation confirming that it will introduce a new "Knowledge Intensive Company" Enterprise Investment Scheme ("EIS") Fund structure. Significant personal tax breaks are available to UK tax-paying individuals who subscribe for shares in EIS qualifying companies, making access to funding much easier for those companies. Following on from changes announced in last year's Budget to relax various qualifying criteria for Knowledge Intensive Companies (or "KICs"), this latest announcement on the launch of a dedicated fund structure is also very good news for biotech companies who are more likely than other companies to satisfy the relevant conditions. This should increase investment into small and growing life science companies.

To help incentivise funding into larger-scale enterprises, the Government announced a consultation to explore options for pooled investment in patient capital. The British Business Bank, Aviva, HSBC, L&G, NEST, The People's Pension, and Tesco Pension Fund will all participate. With total assets under management expected to exceed £1 trillion by 2025, defined contribution pension schemes could be a significant source of capital for scaling biotech companies.

R&D tax credit restrictions

The Budget included statements that the payable R&D tax credit that a qualifying loss-making company can receive in any tax year

will be restricted to three times the company's total PAYE and NICs liability for that year. This change will come into effect from 1 April 2020. This will be of concern to small bioscience companies, particularly those that outsource R&D, whose cash flow could suffer. Companies will still be able to claim payable credit up to the cap, with any unused losses carried forward to be set against future profits.

Changes to Entrepreneurs' Relief ("ER")

ER reduces capital gains tax for founders and certain other employee shareholders on the disposal of shares and some other business assets from 20% to 10%. There are various qualifying conditions, including a minimum holding period and a minimum 5% shareholding (in most circumstances). The minimum holding period will be extended from 12 months to 2 years from 6 April 2019 but there will also be a relaxation to the 5% rule so that qualifying shareholders can keep part of their tax relief where the company takes on external investment and their holding is reduced below 5%.

In addition, with effect from 29 October 2018, a new "economic test" has been introduced requiring shareholders to be entitled to at least 5% of distributable profits and net assets of the company (in addition to holding at least 5% of the ordinary share capital when tested by nominal value and 5% of the voting rights). This has been introduced to combat common ER structuring schemes but could have wide-ranging consequences, particularly for companies with complicated share structures, which is not uncommon in businesses (such as biotech) where heavy up-front investment is needed and often obtained from different sources.

Update to the intangible fixed assets regime

In early 2018, the Government consulted on how the tax treatment of acquired intangible assets could be made more competitive. The Budget announced the introduction of targeted relief for the cost of goodwill (the amount paid for a business that exceeds the fair value of its individual assets and liabilities) in the acquisition of businesses with eligible intellectual property from April 2019. With effect from 7 November 2018, the Government will also reform the de-grouping charge rules, which apply when a group sells a company that owns intangibles, so that a charge will not arise where de-grouping is the result of a share disposal that qualifies for the "Substantial Shareholding Exemption" (a complete relief from tax on the proceeds of a share disposal).

Support for investment in buildings & facilities

The Government will increase the Annual Investment Allowance to £1 million for all qualifying investment in plant and machinery made on or after 1 January 2019 until 31 December 2020, to help stimulate business investment. The Budget announcement also included a proposal to introduce a new form of capital allowances: Structures and Buildings Allowance ("SBA"). SBA will provide relief (at 2% per year over 50 years) for construction expenditure on new non-residential structures and buildings where construction contracts have been entered into after 29 October 2018. Both of these tax developments could help biotech companies with significant capital projects, particularly where the relevant expenditure fails to qualify for the research and development allowance.

Quick facts

about our life sciences practice

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.

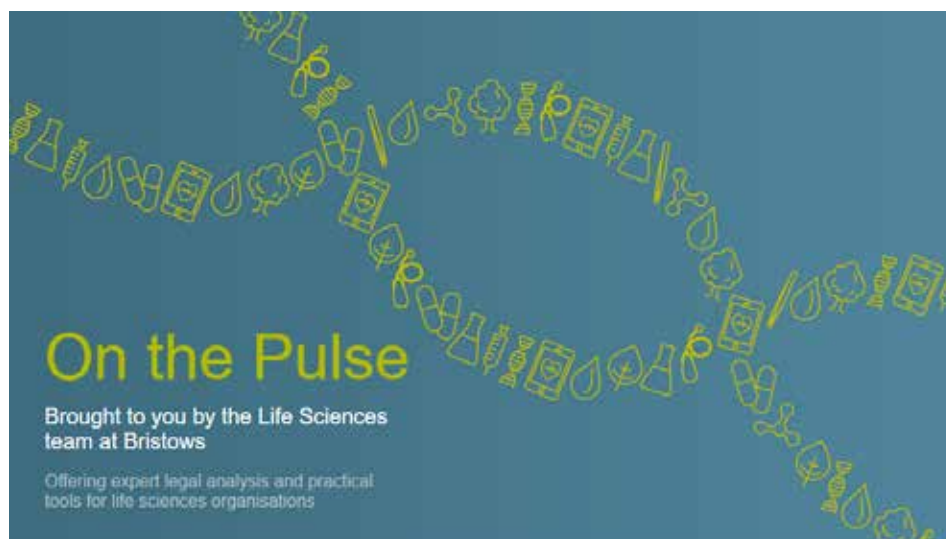
Our clients range from multinational pharmaceutical and biotech companies and medical device manufacturers to universities, SMEs and technology start-ups, private equity and venture capital investors.

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.



Laura Anderson and Liz Cohen, our life sciences sector co-heads

Bristows On the Pulse



Our dedicated Life sciences microsite, On the Pulse, is now live at www.bristowsonthepulse.com

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