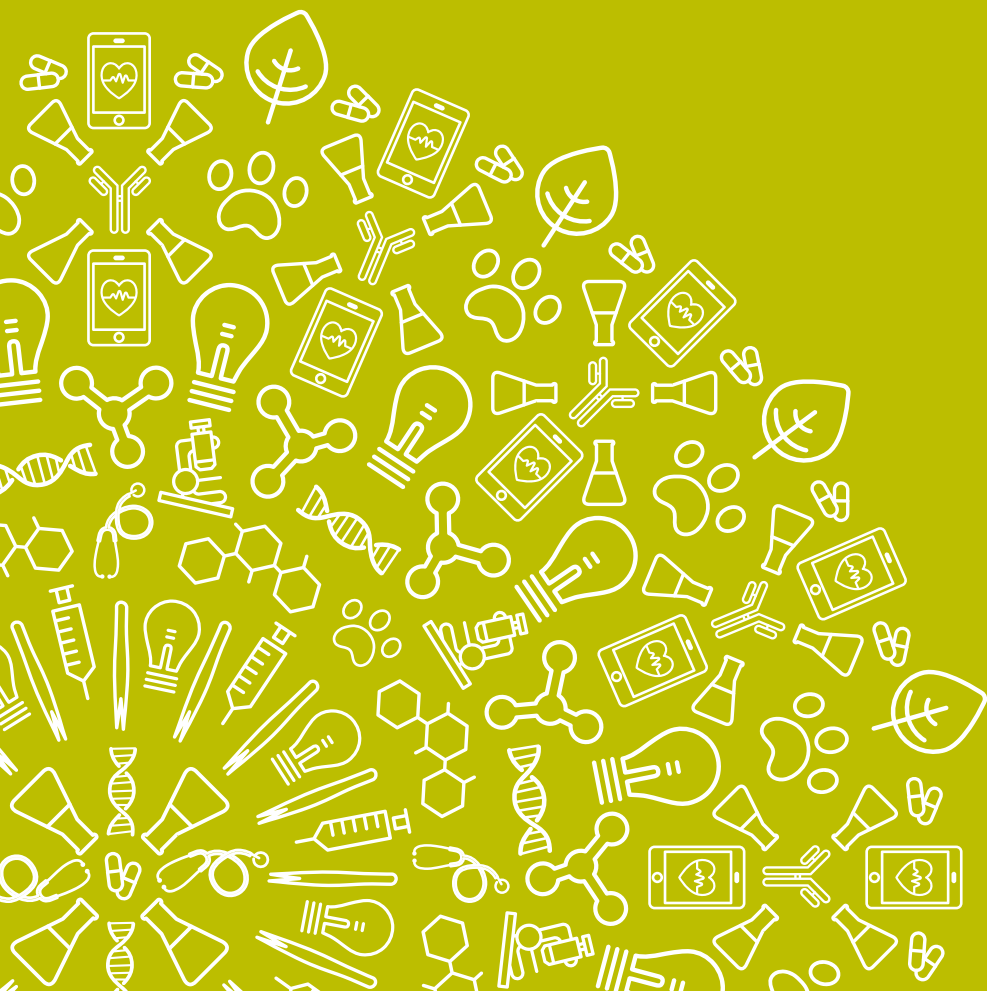


BRISTOWS

BIOTECH REVIEW

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Index

1	Introduction	17	Tax
			Recent tax developments
2	Figures	18	Commercial IP
			CAR-T therapy: the current landscape
3	Patent Litigation	20	Regulatory
	US: Sandoz v Amgen		The Advanced Therapies Manufacturing Action Plan – retaining and attracting advanced therapies manufacture in the UK
4	European Patent Office takes an ‘about turn’ on the patentability of products obtained by essentially biological processes	22	“Is there such a thing as Substitution or Interchangeability for Biosimilars?”
5	The English Patents Court accepts jurisdiction to decide US patent infringement question	24	Corporate
6	Arrow declarations – a new tool for patent litigants?		The lure of the US for UK biotech
7	UK Supreme Court extends scope of patent protection	25	Regenerative medicine sees investment growth in 2017
9	Regulatory process makes patenting pharmaceutical inventions difficult	26	Data Protection
10	Prenatal testing - a case pregnant with issues		The “Genomic Dream”
12	The UPC - an update	27	Secondary1st
13	Competition	28	Movember
	The competition law risks of responding to biosimilars entering the market	29	Q&A
14	Biosimilars: NHS approach to procurement	30	Quick Facts
14	Merger control as a means of protecting and promoting innovation in the life sciences sector	31	Editorial Team
15	Real Estate		
	Science in architecture – the way forward		

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 in the biotech sector in the last 12 months. We therefore include articles on high profile patent cases such as *Actavis v Eli Lilly*, which updates the law in the UK on patent claim construction and formally introduces a doctrine of equivalents in the UK. Being a Supreme Court case, it is binding on all lower UK Courts and will be influential for many years to come. Commentary is also provided on the US Supreme Court decision in *Amgen v Sandoz*, which offers some much needed guidance on the information exchange requirements (the so-called "patent dance") for biosimilar applications. Outside the world of patent litigation, we also report on important issues such as CAR-T therapies, regenerative medicine, data protection and the procurement and substitutability of biosimilars.

This year we have also included an update on Secondary 1st and Movember, two of the charities Bristows supports and that act in the life sciences sector. Secondary 1st is a charity that is particularly close to our hearts, as it was founded in honour of our great friend and colleague, Rosie Choueka. Massive thanks to everyone who has contributed to our fundraising initiatives.

Thanks are also due to Dr Dev Kumar, Head of Legal and Compliance for EUSA Pharma for agreeing to feature in this year's Q&A piece, and to all our authors and support team who make this publication happen.

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



Dr Robert Burrows
Partner
robert.burrows@bristows.com

Robert is a Partner in Bristows' Intellectual Property Department. He is very experienced in patent litigation matters in the UK, particularly for clients within the life sciences sector.

Many of the cases he has managed in recent years have required the coordination of parallel proceedings in multiple jurisdictions within Europe and elsewhere in the world in order to ensure that consistent and optimal arguments have been deployed in all jurisdictions.

The national and international cases with which he has been involved have required, inter alia, preparation for and attendance at preliminary injunction and main action proceedings in numerous countries within Europe and attendance at inspections of pharmaceutical manufacturing processes in India and Japan.

In addition to his litigation experience, Robert regularly assists clients with freedom to operate advice. Robert has a PhD in molecular genetics and has worked for a company specialising in DNA sequencing products.

Biotech Figures

Figures

Biotech landscape in Europe and the UK

There are now **1,155** Biotech companies in the UK. **Other services and suppliers, Therapeutics and Contract Research manufacturing** make up the majority at **22.3%, 16.%** and **15.2%** respectively.

(Source: UK Biotech database)

The UK is on track to becoming the worlds third biotech cluster, raising more venture capital than San Diego in 2016.

(Source: The UK BioIndustry Association 2017)

Last year saw growth of **19%** in revenue generated in the European biotechnology market, growing from **\$22.8b** to **\$27.2b**

(Source: EY Biotechnology Report 2017)

A total of **£1.13bn** was raised by UK-based biotech companies from private and public sources in 2016. Of this, **£681m** was in venture capital funding, **£105m** was in IPO activity and **£344m** came from all other public financing.

(Source: The UK BioIndustry Association 2017)

In 2016, The UK held the most financings of any European market (**78**), the highest total innovation capital financing (**US\$1.3 billion, 25%** of the total) and highest total venture financing (**US\$590 million, 30%** of all European venture capital).

(Source: EY Biotechnology Report 2017)

Last year there were a total of **67,460** employees in **259** public Biotech companies in Europe. This is a **39%** growth in employment and a **9%** growth in the number of public companies from 2015.

(Source: EY Biotechnology Report 2017)



Patent Litigation

Patent Litigation at Bristows

The majority of Bristows' IP lawyers have scientific or technology backgrounds, including physics, chemistry, biotechnology, electronics, engineering 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.

US: Sandoz v Amgen



Dr Dominic Adair
Partner



Thomas Hendicott
Associate

As biological drugs continue to replace small molecules as the sales leaders in the pharmaceutical field, they are increasingly taking the centre-stage in pharmaceutical litigation. However, compared to the established route for approval and launch of small molecule generics, the landscape in relation to biosimilars is still being shaped. In Europe, the basic framework of rules remains largely the same but in the US, recent legislation provides rules which are opaque and considerably different to the small molecule pathway under the Hatch-Waxman Act. This brief article will provide an update on the ongoing US Sandoz Inc v Amgen Inc (filgrastim) litigation¹ in which the Supreme Court has recently rendered a decision providing some clarity in this burgeoning area.

This case considered certain aspects of the abbreviated pathway for obtaining FDA approval of a biosimilar under the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA") – enacted to promote access to affordable medicines as part of Obamacare – and, in particular, the procedures contained therein for resolving patent disputes between biologics innovators and biosimilar applicants, involving what is known as the "Patent Dance". The Patent Dance is an information exchange process between the parties, triggered once the FDA has confirmed that it will review an application. In essence, during the dance, the parties exchange information, including a copy of the biosimilar application and manufacturing information (the "Information") in order to identify relevant patents held by the innovator.

There then follows two phases of potential litigation:

- The first phase, in which the innovator asserts some of the patents identified during the dance; and
- The second phase, triggered when an applicant gives 180 day notice in advance of first commercial marketing of the biosimilar, allows those patents which weren't litigated in the first phase to be asserted by the innovator.

On the basis that these phases are triggered by acts of the applicant, in theory, this legislation allows a biosimilar applicant to clear the way for its biosimilar product during the 12 years of regulatory exclusivity (4 years' data + 8 years' market protection) granted to the innovator under the BPCIA legislation. However, given the number of secondary patents that often surround a successful innovator biologic product, it remains to be seen whether the clearance mechanism can be fully effective. Few biosimilar applicants have so far successfully navigated the new pathway.

One of the first applicants to engage with the BPCIA legislation, and hence one of the most advanced litigation cases to date, is the filgrastim litigation between Sandoz and Amgen. This was the first case to call into question whether the Patent Dance was compulsory, and when exactly the 180 days notice of first marketing should be given.

Before reaching the Supreme Court, the case progressed through the Northern District of California and then the Federal Circuit. The Federal Circuit held that the Patent Dance was not compulsory but that the 180 day notice of first marketing must always be given and only once product approval had been granted by the FDA, effectively forcing biosimilars to wait an additional 6 months before hitting the market.

Both parties filed writs of certiorari, effectively a review petition, to the Supreme Court, Sandoz seeking a review of the Federal Circuit decision on the 180 day notice point and Amgen a review of the decision on the Patent Dance being optional (i.e. must Sandoz provide Information?). The Supreme Court therefore considered two aspects in relation to the Patent Dance, namely whether Amgen were entitled to an injunction:

- (1) to enforce provision of Information which Sandoz had refused to provide; and
- (2) to prevent product launch for 180 days after notice was given following FDA approval (Sandoz had provided notice twice, originally on submission of the FDA application that it intended to market the product upon receiving FDA approval (the "First Notice") and subsequently following receipt of the FDA approval (the "Second Notice")).

In a unanimous decision, the Supreme Court held that failure to provide Information not only deprives the applicant of the certainty that could have been obtained by "dancing" the Patent Dance but the BPCIA specifically provides a remedy for such a failure as the

Patent Litigation

control over the scope and timings of the Patent Dance shifts from the applicant to the innovator as the latter may bring an action for a “*declaration of infringement, validity, or enforceability*” which would not “normally” be available until the second phase of the Patent Dance. Accordingly, under federal law, it was held that an injunction was not an appropriate remedy. Hence, no compulsion for the biosimilar applicant to dance and provide Information. However, it should be noted that the question was left open for the Federal Circuit to decide on remand whether an injunction is available as a matter of the relevant state law, or whether a state-law injunction may be precluded by federal law.

The second point was also found in favour of Sandoz. The Court held that the statutory context only provided for a single timing requirement (**180 days before marketing, in line with the First Notice**) as opposed to two timing requirements (after licensing and 180 days before marketing, in line with the Second Notice) such that the **First Notice was valid** and the Federal Court had erred in granting an injunction until 180 days after the Second Notice.

This decision provides clarity on two key aspects of the Patent Dance which should assist biosimilar applicants in the US moving forward. First, whether applicants wish to participate in the Patent Dance at the expense of providing sensitive information or risk ceding control of the process to the originator. Second, and arguably more importantly, a biosimilar applicant is able to provide notice **prior to** receiving FDA approval. This, in effect, prevents a *de facto* 180 day extension to market exclusivity, or what Judge Chen had described in the Federal Circuit decision as “*an extra-statutory exclusivity windfall*”.

In a separate development in US biosimilar litigation, Amgen was recently awarded \$70 million in damages in a patent infringement suit against Hospira in relation to Hospira’s biosimilar Epogen® (active ingredient EPO)². This was one of the first BPCIA cases to reach trial. Hospira’s EPO product has not yet been approved, but 21 batches had already been manufactured prior to imminent expiry of the patent in suit. Hospira argued that its production of EPO was protected by the ‘Bolar’ statutory safe harbour that allows for use of patented processes for the purpose of obtaining FDA approval. The jury disagreed, holding that 14 of the 21 biosimilar EPO batches infringed.

¹ 582 U.S. ____ (June 12, 2017)
² Case 1:15-cv-00839-RGA

European Patent Office takes an ‘about turn’ on the patentability of products obtained by essentially biological processes



Gemma Barrett
Partner

Article 53(b) of the European Patent Convention (EPC) excludes from patentability ‘*essentially biological processes for the production of plants or animals*’ but makes no mention of products derived from such processes. Following a period of considerable uncertainty in relation to whether such products are patentable, the matter now seems to have been clarified by the European Patent Office (EPO) publishing earlier this year a notice stating that from 1 July 2017 plants and animals exclusively obtained by means of an essentially biological process will no longer be patentable.

This decision represents a U-turn for the EPO following the decisions of the Enlarged Board of Appeal (EBA) in 2015 in the Tomato II and Broccoli II cases (G2/12 and G2/13). In these cases the EBA conducted a lengthy and in-depth legal analysis leading to the conclusion that a narrow interpretation of Art 53(b) EPC was appropriate and as a result plants and animals derived from essentially biological processes were in principle patentable, even if they were inevitably derived from such processes.

Following the EBA decision the law seemed settled until the European Parliament asked the EU Commission to consider various issues concerning the Biotech Directive (Directive 98/44/EC). The exclusion to patentability in the Biotech Directive is framed much like that in Article 53(b) EPC i.e. it expressly excludes from patentability essentially biological processes for the production of plants and animals but does not mention products derived from such processes. The Commission reviewed the context and provisions of the Biotech Directive and published a notice on 3 November 2016 (Notice 2016/C 411/03³) concluding that the European Union legislators’ intention when adopting the Biotech Directive was to exclude such products from patentability.

This decision, in direct conflict to that reached by the EBA in Tomato II and Broccoli II, left the EPO in a difficult position. The Commission’s Notice states that it is intended only as guidance and, in any event, even the EPO is not bound by the views of the Commission nor any decision of the Court of Justice of the European Union (CJEU) on the interpretation of the Biotech Directive. However, the application and interpretation of the Biotech Directive would fall to the courts of European Union member states and this would leave national courts enforcing granted patents having to resolve the conflict themselves and decide whether to follow a seminal EBA decision or the guidance notice from the European Commission. A reference to the CJEU seemed inevitable in such circumstances. In addition, the Biotech Directive is itself relevant to the EPO when considering patentability. The EPC Implementing Regulations were amended to include its main provisions and it is used as a supplementary means of interpretation (see Rule 26(1) EPC).

In response to the EU Commission Notice, the EPO at the end of 2016 stayed all proceedings in relevant examination and



opposition cases *ex officio*. This remained the situation until the EPO published its notice clarifying that plants and animals exclusively obtained by means of an essentially biological process will no longer be patentable. The EPO notice states that the decision was taken by the Administrative Council to safeguard uniformity in harmonised European patent law. It seems the EPO wanted to avoid future divergent decisions on this issue.

Following the EPO notice the Administrative Council has amended Rules 27 and 28 of the Implementing Regulations to the EPC and these changes came into force on 1 July and apply to European patent applications filed on or after this date, as well as European patent applications pending at that time. The key provision in Rule 28(2) now reads:

"(2) Under Article 53(b), European patents shall not be granted in respect of plants or animals exclusively obtained by means of an essentially biological process."

3 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:LJOC_2016_411_R_0003&from=EN

The English Patents Court accepts jurisdiction to decide US patent infringement question



Dr Gregory Bacon
Partner



Katie Rooth
Associate

The English courts have recently been willing to accept that they have jurisdiction to consider certain matters relating to foreign IP rights, including patents, so long as questions of validity are not in issue⁴. This trend was continued in the case of *Chugai v UCB*⁵, which concerned the scope of a patent licence.

Chugai sought a declaration that it was no longer obliged to pay royalties under a licence with UCB relating to a bundle of patents for tocilizumab products. Chugai sells tocilizumab, an interleukin-6 monoclonal antibody, as Actemra for rheumatoid arthritis and other inflammatory diseases. The licence originally covered multiple patents but as of January 2016 only one, a US patent, remained in force. Chugai was of the view that its products did not fall within the scope of the remaining US patent and therefore sought a declaration that it no longer owed royalties under the licence. The licence in question had an English governing law and exclusive jurisdiction clause, and Chugai sought the declaration from the English Patents Court.

Chugai's non-infringement case included arguments on the correct construction of the patent under US law, including that the US patent would lack novelty on the claim construction advanced by UCB due to prior art that was before the USPTO during prosecution. Chugai therefore sought to run a squeeze between infringement and validity in order to support its argument for the narrower construction. On the other hand, Chugai did not seek relief on validity and limited the relief sought to a declaration that royalties were no longer payable. UCB resisted Chugai's claim and applied to strike out those parts

of the particulars of claim that allegedly related to the validity of the patent. UCB argued that although the claim was framed as a declaration relating to a contract between the parties, Chugai was seeking to bring the validity of a foreign patent in by the back door. As the English court has no jurisdiction to consider validity of foreign IP rights (under the *Moçambique* rule, so-named after the case of *British South Africa v Companhia de Moçambique*⁶ and as applied in subsequent cases), UCB argued that the court should strike out those parts of the particulars of claim that raised issues of invalidity on the basis that they were not justiciable before the English courts.

The judge, Mr Justice Henry Carr, rejected UCB's strike-out application. He compared the situation to the earlier case of *Celltech v Medimmune*⁷, where the Court of Appeal held that the parties to a licence had agreed to give jurisdiction to the English courts concerning the scope of licensed patents, regardless of whether arguments would be raised concerning the effect that different constructions of the scope of protection would have on validity. In that case, the Court of Appeal had stressed the commercial importance of exclusive jurisdiction clauses in patent licences and of requiring parties to keep their agreement. This was particularly so given that having a single court decide all questions of infringement (and thus the scope of the licence) would lead to a greater chance of consistency.

The judge also rejected UCB's argument that the court should decline jurisdiction under the *Moçambique* rule, on the basis that the current dispute was not primarily about validity. In the judge's view, the *Moçambique* rule only applied to proceedings that primarily concerned questions of validity of a foreign patent. As Chugai were not contending that the patent was invalid, or seeking relief in relation to validity, its claim was correctly characterised as a contractual claim and the validity issues were limited to the assessment of the scope of the US patent's claims. Furthermore, as the parties had agreed that disputes should be determined by the English courts, it was not an affront to comity to give effect to that agreement. The trial of the action between Chugai and UCB has since been fixed to be heard in February 2018, which we will no doubt report on in next year's Biotech Review.

This recent case, wherein the English court has recognised jurisdiction over questions relating to foreign patents, follows recent jurisprudence as described above in the introduction. It can be contrasted with the earlier case of *Anan Kasei v Molycorp*⁸, where a claim to infringement of a German patent was declined by the English court. In that case, the defendant challenged validity of the German patent in Germany. The issue between the parties was therefore whether the defendant was infringing a valid claim of the German patent. As these were inseparable sub-issues (for example on construction of the patent claims), the English court declined to accept jurisdiction over infringement.

⁴ e.g. *Lucasfilm v Ainsworth* [2011] UKSC 39 and *Activis v Eli Lilly* [2011] EWHC 3316 (Pat)

⁵ [2017] EWHC 1216 (Pat)

⁶ [1893] AC 602

⁷ [2004] EWHC 152

⁸ [2016] EWHC 1722 (Pat)

Arrow declarations – a new tool for patent litigants?



Dr Laura von Herten
Associate

In last year's edition we reported on the comeback of the *Arrow* declaration, with two decisions of the English Patents Court recognising that the jurisdiction to grant such declarations existed. This year saw the continuation of these actions, with the Court of Appeal confirming the availability of the declarations, and the Patents Court granting them at trial.

An *Arrow* declaration is a declaration that a particular product (or process) would have been anticipated and/or obvious at a given date. Its main purpose is to provide a defence to an alleged patent infringer, in that such a product (or process) could not infringe any valid patent with the same priority date, regardless of the form of the claims of the patent (a version of the so-called *Gillette* defence). The name derives from *Arrow Generics v Merck* [2007] EWHC 1900 (Pat), in which such a declaration was first sought.

The present dispute concerned AbbVie's monoclonal antibody adalimumab, sold under the brand name Humira®. Fujifilm Kyowa Kirin Biologics (FKB) and Samsung Bioepis/Biogen Idec (S/B) had been developing their own biosimilar versions of adalimumab. The compound patent protection for adalimumab expires in October 2018. However, AbbVie owned a number of "follow-on" patents and patent applications protecting dosage regimens, formulations and uses of adalimumab.

Therefore, as encouraged by the English courts, FKB, and at a later stage S/B (who was joined as a claimant to the first of two actions commenced by FKB, being actions FKB 1 and FKB 2), commenced proceedings to "clear the way" for their biosimilar adalimumab medicines prior to the date of expiry of the SPC on the compound patent.

They sought to revoke granted patents to dosage regimens for adalimumab. However, in light of pending divisional applications at the EPO covering the same subject matter, and AbbVie's threat of patent infringement actions against biosimilar competition throughout the world, FKB and S/B also sought *Arrow* declarations that those specific dosage regimens would have been obvious at each of the claimed priority dates of the patents in suit. In the course of the proceedings AbbVie abandoned those patents in the UK, making it impossible for the revocation actions to proceed, whilst at the same time continuing to file and/or maintain further divisional applications at the EPO.

In 2016, following applications from AbbVie to have the claims for the *Arrow* declarations struck out, Henry Carr J (in two separate judgments in FKB 1) and Arnold J (in FKB 2) both held on a summary basis that the jurisdiction to grant *Arrow* declarations arguably existed.

Court of Appeal – *Arrow* declarations are available in principle

The first judgment in FKB 1 and the judgment in FKB 2 were subject to a joint appeal, which the Court of Appeal ruled upon in January 2017.

AbbVie had contended that actions for *Arrow* declarations were, amongst other things, precluded by section 74 of the Patents Act 1977, because they put the validity of a patent in issue.

It also argued that such declarations were a collateral attack on the proceedings within the EPO, and that to allow them would be to open the floodgates.

The Court of Appeal reviewed the statutory framework, noting that section 74 of the Patents Act limits the proceedings in which it is permissible to put the validity of a patent in issue, and that neither the Patents Act nor the European Patent Convention permits pre-grant opposition. Nevertheless, the Court concluded that there was no issue of principle which prevented the granting of *Arrow* declarations in appropriate cases. In doing so it held that:

- i) a declaration that a product, process or use was old or obvious at a particular date did not necessarily offend against section 74 of the Act;
- ii) such a declaration may offend against the Act where it is a disguised attack on the validity of the granted patent;
- iii) such declarations do not offend against the scheme of the EPC or the Act simply because the declaration is sought against the background of pending divisional applications by the counter-party;
- iv) On the other hand the existence of pending applications cannot itself be a sufficient justification for granting a declaration;
- v) Whether such a declaration is justified depends on whether a sufficient case can be made for the exercise of the court's discretion in accordance with established principles.

Having held that the discretionary power exists, the Court of Appeal left it to the Patents Court to develop the principles for its exercise in more detail. However, it stressed that the statutory proceedings for revocation should be regarded as the normal vehicle for obtaining any desired finding of invalidity.

Nonetheless, in the case at hand, the Court said that it was at least open to interpretation that AbbVie was deliberately trying to shield the claims of its patents from scrutiny in the EPO and in the national court. Had the patents not been abandoned, FKB would have had the opportunity to seek findings of invalidity in the usual way. Because of AbbVie's apparent conduct, there was a case for the court to intervene by way of declaration to provide FKB with a measure of useful commercial certainty.

The Patents Court grants *Arrow* declarations

The trial on the merits in FKB 1 was heard by Henry Carr J a few weeks after the Court of Appeal judgment was handed down. The Judge found that, on the evidence provided at trial, the dosage regimens in question were known or obvious at the relevant priority dates. He therefore proceeded to consider whether, on the particular facts of the case, the Court's discretion for granting the declarations sought should be exercised.

Applying *Financial Services Authority v Rourke* [2002 C.P. Rep. 14] in which the Court held that when considering whether to grant a declaration, the court should take into account: (i) justice to the claimant; (ii) justice to the defendant; (iii) whether the declaration would serve a useful purpose; and (iv) whether there are any other special reasons why or why not the court should grant the declaration – the Judge held that, in the unusual circumstances of the case, it was in the interests of justice to grant the declarations sought.

Patent Litigation

On the question of whether the declarations would serve a “useful purpose”, the Judge held that the test should be whether the declarations would serve a useful purpose in the UK (he held that a declaration that is sought solely for the benefit of foreign courts would rarely be justified). AbbVie had argued that the declarations sought would serve no useful purpose in the UK because it had offered undertakings that it would not obtain any patent protection in the UK that would be infringed by their biosimilar products as a result of their use in accordance with the relevant dosage regimens.

However, the Judge disagreed and held as follows. First, the declarations would dispel the commercial uncertainty in the UK (and European) market, which AbbVie’s threats of patent infringement actions had created. He referred to the clarity that such declarations would provide to third parties in the UK seeking to do business with FKB and S/B. Second, the declarations would protect FKB and S/B’s supply chain for the UK market. Third, he held that the declarations would also promote settlement.

The “special reasons” identified by the Judge, on the “most unusual facts of this case” included: (i) AbbVie’s conduct of threatening infringement proceedings whilst abandoning patents in validity proceedings at the last moment (in order to shield its patent portfolio from scrutiny); (ii) the amount of money at stake for FKB and S/B in terms of the investment they had put into clinical trials and also the threat of having to pay damages if they launched at risk (Humira is the world’s top-selling drug); and (iii) the need for commercial certainty, having regard to AbbVie’s threats to sue for infringement throughout the world.

The trial on the merits in FKB 2 was due to be heard in a window floating from May to July 2017, but settled before trial.

Conclusion

The English Courts have confirmed that the *Arrow* declaration stands as a new, Court-approved, tool available to litigants. However, notwithstanding that such declarations were granted in this particular case, the remedy is discretionary and it remains to be seen how the Patents Court further will develop the principles for the exercise of this discretion.

It is clear that *Arrow* declarations are not available in relation to granted patents, for which the statutory remedy for revocation should be regarded as the normal vehicle for obtaining any finding of invalidity. Furthermore, in most circumstances, such declarations will also not be available in relation to putative future patents. Thus, Floyd LJ stated at paragraph 93 of the Court of Appeal judgment:

“A claimant cannot seek an Arrow declaration simply because it would like to know whether a patent application in the course of prosecution will result in a valid patent. The course envisaged by the statute is that he should wait and see what, if any, patent is granted.”

That said, *Arrow* declarations will in principle be available where the statutory remedy is being frustrated by shielding subject matter from scrutiny in the English Court. However, in such instance a claimant will still need to show that a sufficient case can be made for the exercise of the Court’s discretion in accordance with established principles.

In a recent decision in *Generics (UK) v Yeda* [2017] EWHC 2629 (Pat) – the first case in which *Arrow* declarations have been considered since FKB1 – Arnold J declined to grant such a declaration, despite pending divisional applications covering the same subject matter as the patent at issue. On the facts of the case, the defendants had not sought to shield the subject matter of the patent from scrutiny in the English Court and had defended the revocation action, and the judge was of the view that an *Arrow* declaration would not have provided the claimants with greater relief (in terms of spin-off value or commercial certainty) than the reasoned judgment on the validity of the patent at issue. The case confirms that *Arrow* declarations will only be granted in exceptional circumstances. A potentially interesting side note to this decision is that Arnold J held the claimants’ dosage regime (the subject of their *Arrow* declaration) to be obvious even though the declaratory relief was refused. Such a finding of obviousness was inevitable in this case, as it was accepted that the dosage regime infringed the patent in suit, which was itself held to be obvious. It remains to be seen whether the courts will also pronounce upon the obviousness of products and/or processes in circumstances where the patent in suit is not infringed (or there is no patent in suit), and the request for an *Arrow* declaration in respect of said product and/or process is refused.

Supreme Court extends scope of patent protection



Dr Gregory Bacon
Partner

In the *Activis vs Eli Lilly* judgement from July of this year, the Supreme Court reintroduced a true form of the doctrine of equivalents into UK patent law, allowing Lilly’s appeal and holding that its patent relating to pemetrexed was infringed both directly and indirectly in the UK, France, Italy and Spain⁹.

Eli Lilly’s patent claimed use of a composition comprising pemetrexed disodium and vitamin B12 for treatment of tumour growth, as either Swiss-type or EPC 2000 claims. In its multiple DNI actions, Actavis had sought to argue that its generic pemetrexed/vitamin B12 products did not infringe on the basis that they contained either pemetrexed diacid, pemetrexed dipotassium or pemetrexed ditromethamine but not the disodium salt. The Courts at first instance and on appeal had held that Actavis did not directly infringe the claims as the claims in question were limited to the disodium salt, albeit that the Court of Appeal had overturned the Patent Court’s finding on indirect infringement in holding that these products infringed when reconstituted in saline for injection as pemetrexed disodium was formed from the pemetrexed anion and the sodium cation in solution.

The Supreme Court’s decision turned on the question of whether a variant could be held to infringe a patent claim. In doing so, the Court decided the role of equivalence in determining the scope of protection. Relying on the approach in other European countries, the Supreme Court (with Lord Neuberger giving judgment on behalf of the Court) decided that Lord Hoffmann’s approach to the issue in *Kirin-Amgen*¹⁰ was not entirely correct. In the Court’s opinion, the question of infringement in a case of variants was best considered by addressing two issues: (i) does the variant infringe any of the claims as a matter of normal

Patent Litigation

interpretation?; and, if not (ii) does the variant nonetheless infringe because it varies from the invention in a way or ways which is or are immaterial? This approach was held to comply with Article 2 of the Protocol on Article 69 as issue (ii) raises the principle of equivalents, but limits its ambit to those variants which contain immaterial variations from the invention. The Court was of the view that Lord Hoffmann in *Kirin-Amgen* had erred by conflating these two issues into a single question of interpretation.

In determining the answer to the first question, the applicable principles were clear and followed those of construction of documents generally (including contracts). On that basis, Actavis' products did not directly infringe as in no sensible way could Actavis' products be said to fall within the expression "pemetrexed disodium". In deciding whether a variant was immaterial, the Supreme Court revisited the 'Improver' or 'Protocol questions'. Importantly, the Court reformulated the second of these questions as in its view the second question had been improperly applied previously and by the Courts below. The reformulated questions are:

i) *Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, ie the inventive concept revealed by the patent?*

ii) *Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?*

iii) *Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?*

In order to establish infringement in a case where there is no literal infringement, a patentee would have to establish that the answer to the first two questions was "yes" and that the answer to the third question was "no".

The significant change with this reformulation is that it introduces hindsight into the determination of the second question, as the skilled person is now assumed to know that the variant achieves substantially the same result as the invention and the patentee is not required to demonstrate this in the patent or on the basis of the skilled person's common general knowledge. The Supreme Court came to this conclusion on the basis that the previous incarnation of the second Protocol question imposed too high a burden on the patentee as it required the skilled person to work out for themselves whether the variant would work. That had an impact on the facts of the case before the Court, as it had been held that although the skilled person would not know which other pemetrexed salts would have acceptable properties for use in the claimed combination, it was a routine exercise to conduct salt screening to determine that question. Further reasons for this approach were that it was held to be consistent with the approach of the German, Italian and Dutch Courts and that it could apply to variants that rely on, or are based on, developments which occur after the priority date.

Having applied the reformulated questions, the Supreme Court was of the preliminary view that Actavis' products would fall within the scope of protection of the patent as immaterial variants and thus that the DNIs sought should be refused. Nevertheless, it

went on to consider whether the prosecution file should lead to a different conclusion.

Actavis sought to rely on the prosecution history on the basis that the patentee had previously tried to obtain protection for the claimed combination with any pemetrexed compound and that this had been rejected by the EPO on the basis that it introduced subject matter contrary to Article 123(2) EPC. The Supreme Court held that reference to the prosecution file would only be appropriate where (i) the point at issue is truly unclear if one confines oneself to the specification and claims of the patent, and the contents of the file unambiguously resolve the point, or (ii) it would be contrary to the public interest for the contents of the file to be ignored. Neither situation arose here. Further, although only *obiter*, the Court was of the view that even if the examiner had been right that the wider claim would add subject matter, that consideration did not have any bearing on the question of whether any pemetrexed salts other than pemetrexed disodium should be within the scope of the patent pursuant to the doctrine of equivalents. According to the Court: *"The whole point of the doctrine is that it entitles a patentee to contend that the scope of protection afforded by the patent extends beyond the ambit of its claims as construed according to normal principles of interpretation"*.

This has the interesting potential consequence that infringement and validity appear to have become uncoupled in a way that is unfamiliar to the (modern) UK patent practitioner. For example, it may be that infringement and novelty are no longer two sides of the same coin and there is no longer an absolute *Gillette* defence to working the prior art. It is an interesting thought experiment to imagine whether the Supreme Court would have reached the same conclusion if validity on these types of questions had been in issue. This point was raised in the recent case of *Generics (UK) v Yeda*¹¹. Although the case was decided on other issues, Mr Justice Arnold's *obiter* view was that a claim lacked novelty only if the prior art disclosed subject matter which fell within the claim on its proper interpretation and that it was not appropriate to ask whether that disclosure would have infringed the patent in light of the extension of protection provided under the doctrine of equivalents. As the Supreme Court had not addressed the question of novelty, the test for which had been set out by the then House of Lords in *Synthon v SmithKline Beecham*¹², it would require another decision of the Supreme Court to give a definitive answer.



In light of the above, Actavis' cross-appeal on indirect infringement was of little relevance to the outcome. Nevertheless, it is worth noting that the Court dismissed this appeal and that in doing so it made an interesting observation in relation to infringement of Swiss-type medical use claims. In this case Actavis had argued that as the pemetrexed disodium only existed after dissolution of their pemetrexed product in saline by the clinician prior to administration, the pemetrexed disodium formed was part of the medicament but not used in the manufacture of a medicament and thus the Swiss-type claims were not indirectly infringed. The Court dismissed this argument, holding that although the pemetrexed disodium came into the manufacturing process later than it would have if the original medicament included pemetrexed disodium rather than a different salt, before the medicament was administered to the patient it did include pemetrexed disodium and vitamin B12.

The judgment comes as a surprise to many, as the previously established UK case law had over time firmly done away with the idea of 'pith and marrow' infringement, culminating in the seminal House of Lords judgment in *Kirin-Amgen* where Lord Hoffmann had explained that the correct approach to claim construction was to abandon literalism in favour of purposive construction and that Article 69 EPC prevented equivalence from extending protection outside the claims even if it could be used to construe the scope of those claims under purposive construction. The implication of the decision, not only in terms of construction and infringement but also validity, will be played out in years to come.

As a post-script, notwithstanding that the Supreme Court held that the Italian designation of the European patent was infringed under the Italian law on the doctrine of equivalents, Eli Lilly was subsequently unsuccessful in asserting that patent in interim proceedings in Italy against a different party (*Fresenius*)¹³. In that case the Court of Milan held that it was not bound by the decision of the UK Supreme Court as the case concerned different parties and the generic product in question had a different formulation and authorised indications than Actavis' pemetrexed ditromethamine product that was the subject of the UK action. The Italian Court decided to rely on the EPO file history, contrary to the approach of the UK Supreme Court, in holding that there was a clear demonstration of a conscious intention of the patentee to limit the claims of the patent to pemetrexed disodium.

Nevertheless a number of other European courts have arrived at the same finding of infringement under the doctrine of equivalents (for example in the Netherlands and Switzerland).

⁹ *Actavis v Eli Lilly* [2017] UKSC 48

¹⁰ *Kirin-Amgen v Hoechst Marion Roussel* [2004] HL 46

¹¹ [2017] EWHC 2629 (Pat)

¹² [2006], [2006] RPC 10

¹³ *Fresenius Kabi Oncology v Ors v Eli Lilly* (N.R.G. 54470/2016)

Regulatory process makes patenting pharmaceutical inventions difficult



Gemma Barrett
Partner



Adrian Chew
Associate

The life sciences industry is well aware of the lengthy and expensive process of obtaining an authorisation to sell a new medicine. What is perhaps less highlighted is how this process interacts with the patent rights for such medicinal products. The Court of Appeal decision in *Hospira v Genentech*¹⁴ is a good example of where the regulatory process has resulted in it being difficult to patent what could very well be considered an inventive discovery.

The *Hospira* decision concerned Genentech's trastuzumab (Herceptin®) which is used in the treatment of HER2 positive breast cancer. This was the third and final decision in a series of cases brought by Hospira to clear the way to launch a biosimilar trastuzumab product in the UK. In this instance, Genentech's patent sought to protect the discovery that when trastuzumab is used in combination with the chemotherapeutic agent paclitaxel, it resulted in a substantial increase in time to disease progression and tumour response rates in HER2-positive metastatic breast cancer patients. The claim at issue was a "Swiss-type" second medical use claim which included as part of its technical subject matter a requirement that the claimed therapeutic benefit was actually achieved.

Hospira attacked the validity of the patent as not being novel or inventive over a review article written by Baselga *et al.* The review article not only discussed the results of previous studies on trastuzumab and paclitaxel used alone and together, but disclosed the design of a Phase III clinical trial of the combination which was said to be ongoing.

At first instance, the Patents Court found that the disclosure of the design of the clinical trial did not mean that the patent was not new, as the skilled person administering the combination would not have the mental element required by the fact it was a Swiss-type claim. This was because he or she could not intend to administer the combination to achieve the clinical benefit as it was not possible to know without the results of the Phase III clinical trial (which were only disclosed in the patent) that the combination would achieve the clinical benefit. However, the Patents Court did find that the Baselga paper made the combination obvious to try with a fair expectation of success and therefore the patent was invalid as it lacked an inventive step.

The Court of Appeal upheld the Patents Court decision. In doing so they rejected Genentech's submission that as the invention of the patent lay in the actual attainment of the clinical benefit (i.e. that the combination was effective as opposed to may be effective) it was necessary for the Court to ask whether the Baselga paper made it more or less self-evident that the combination ought to work. In this regard the Court of Appeal confirmed that there could be no special law (*lex specialis*) for claims which included as a requirement a technical benefit and the law remained whether there was a fair expectation of success, which would be determined based on the facts of each case.

Patent Litigation

In coming to their decision that the invention was obvious, the Court of Appeal noted that the Baselga paper's proposal for a combination would have been logical to the skilled person; combination therapies were well known in the treatment of cancer and there were no convincing reasons why the combination of trastuzumab and paclitaxel would not yield the predicted clinical benefit. This was despite it being accepted that conducting the Phase III clinical trial would be expensive and time consuming, especially for a party other than Genentech, and that the individual publications reviewed in the Baselga paper had themselves not attracted much interest from the scientific community.

What this highlights is the difficulty in obtaining patent protection for discoveries made as a result of clinical trials, a circumstance which is becoming more common with the growing emphasis from the UK Courts on inventions needing to be demonstrated to be plausible when filed. This difficulty arises as once the idea to undertake the clinical trial has been disclosed, it makes it harder to patent a technical advance which relies on the results of the clinical trial as its invention. Whilst in this case the disclosure of the protocol was in a review article, it should not be forgotten that the authorities in Europe and the US are requiring more and more information to be published on proposed and ongoing clinical trials as well as their results (e.g. on ClinicalTrials.Gov).

Whilst currently this issue does not seem possible to circumvent, some mitigation may be possible by taking the following steps:

1. Coordinating obligations to publish information on clinical trials with the filing of patent applications seeking to protect the discovery of such technical advances, in an attempt to limit or delay disclosures which may prevent inventions being patentable;
2. Ensuring that adequate confidentiality provisions are in place to protect the commercially-sensitive information surrounding clinical trials and their results; and
3. As far as possible limiting the scope of the protection sought in the patent to the specific discovery made during the relevant clinical trial, in particular features which could not have been predicted with confidence without the clinical trial being carried out.

14 [2016] EWCA Civ 1185

Prenatal testing – a case pregnant with issues



Brian Cordery
Partner



Rachel Mumby
Senior Associate

On 21 November, Henry Carr J handed down a judgment concerning the validity and infringement of five patents in the field of non-invasive prenatal diagnosis. This technology requires sampling only of the mother's blood in order to test for disorders such as Down's syndrome, rather than previous invasive methods such as amniocentesis which involve sampling cells from the amniotic fluid or placenta. There were a large number of parties involved in what were actually three claims combined into one trial. The first two claims were brought by relevant patentees/licensees against two Premaitha entities and the third was brought against three entities referred to collectively as TDL/Ariosa.

The judgment includes analysis of a great number of different patent law issues, a few of which are identified below. In relation to areas such as obviousness, construction and infringement, as well as priority and enablement, the Judge provided useful summaries of the law which may be of interest to readers.

Priority and enablement

One of the patents, referred to as "Lo 1", disclosed that cell-free DNA could be detected in maternal plasma serum in sufficient quantities for it to be used in prenatal testing. The findings in Lo 1 were published to critical acclaim after the priority date of the patent.

One challenge to the validity of Lo 1 was entitlement to priority/enablement. With respect to enablement, the Judge noted that it is possible to frame a claim in general terms if the teaching of the patent is a principle of general application. However, it was also noted that the claim would be insufficient if it was shown that the invention did not work with substantially everything falling within the claims. TDL/Ariosa decided to run a squeeze argument in relation to infringement and validity – namely, that if the claims of Lo 1 extended to cover one of the alleged infringing tests referred to as the Polymorphic Assay of Harmony then this approach was not enabled in the priority document and hence Lo 1 would not be entitled to priority and would be invalid. However, the patentee argued that Lo 1 claimed a principle of general application and could extend to improvements enabled by technological developments without becoming susceptible to an insufficiency challenge.

Noting that this was a "key issue which requires a detailed analysis of the legal principles", Henry Carr J considered statements of Lord Hoffmann in *Kirin-Amgen*¹⁵ and Lord Neuberger in *Actavis v Eli Lilly*¹⁶ in concluding that: "fairness to the patentee may require that unforeseeable variants, enabled for the first time by new technology, fall within the scope of protection, although the patentee is unlikely to succeed where the variant was unforeseeable at the priority date. A variant which represents an inventive step may nonetheless infringe... It would not make sense if, in those circumstances, the patent was found to be insufficient



solely because such an immaterial variant, which it did not enable, fell within the scope of its claims.” The Judge seemingly drew comfort in his conclusions from two decisions of the EPO TBA – T292/85 (*Genentech I*) and T636/97 (*Erythropoietin II*). On this basis, the squeeze by the Defendants was unsuccessful and he held the claims to be entitled to priority. However, other challenges to priority and insufficiency did succeed in relation to certain but not all claims of Lo 1.

Discovery as such

The claimants argued that on the patentee's construction, claim 1 was in substance a claim to any method involving the discovery that foetal DNA that is paternally inherited and not possessed by the mother is detectable in maternal serum/plasma. They further argued that there were no technical limits imposed on the method of detection. Whilst ultimately it was not determinative, Henry Carr J held that claim 1 was not to a discovery as such, but to a practical process of implementing a discovery, namely a detection method, which had practical applications and was therefore patentable.

Infringement

One of the points of potential confusion in *Actavis v Eli Lilly* (see pages 7-8 of this publication) is the use of the word “normal” in the first limb of the test set out in that case by Lord Neuberger. Henry Carr J agreed with Arnold J in *Generics (UK) v Yeda* (see page 8 of this publication) and held that “normal” in this context means purposive construction.

Prosecution history

As noted on page 8, the Supreme Court in *Actavis v Eli Lilly* held that the Court should take a skeptical but not absolutist attitude to the prosecution history when considering construction and infringement. The Defendants in the present case argued that this would be a case where it would be contrary to the public interest for the contents of the prosecution history to be ignored. In particular, the claims had been amended during opposition at the EPO to overcome an insufficiency finding and Premaitha submitted that the infringement argument advanced by the patentee related to the type of detection that was found by the EPO to be insufficient and which the claim was limited to exclude. Whilst Henry Carr J initially found this to be a “powerful argument”, on further consideration of the file he rejected it on the basis that the type of test which rendered the original claim insufficient was not used in the accused test.

Infringement of process claims

A further point considered was infringement of process claims where part of the process is carried out in the UK and part in another country. Comparing and contrasting the previous decisions of *Menashe v William Hill*¹⁷ and *RIM v Motorola*¹⁸, in the third judgment, the Judge held that the crucial question to ask was: where, in substance, was the alleged infringing process taking place? The steps in the alleged infringing process were summarised as follows:

- i. receiving a blood sample from a patient in the UK;
- ii. carrying out the preparatory steps and the sequencing processes in the UK;
- iii. sending the raw data comprising the results of the sequencing reads electronically to Taiwan;

- iv. performing the analysis of the data in Taiwan, including the Rx calculation, sex determination and foetal fraction estimation;
- v. generating a report in Taiwan;
- vi. sending the report back to the UK; and
- vii. receiving and unpacking the report in the UK and formatting it for printing, storage and sharing with the patient.”

On this basis, the Judge had little hesitation in finding direct infringement that the process of the patent had been used in the UK. Alternative arguments based on, among other things, indirect infringement, were not considered.

Exclusive licence/title issues.

Title issues became important for several of the patents in issue, in particular whether certain parties were true exclusive licensees within the definition of section 130 of the Patents Act 1977 (which would then give them entitlement to sue). One argument raised was that a licence to a party “and its affiliates” meant that that licence could not be exclusive. Henry Carr J agreed with this on the basis that a licence is only exclusive under s130(1) if it is granted to a single person, although he may grant sub-licences to “persons authorised by him”. Further arguments in relation to a different licence were that this licence could not be exclusive as it did not exclude the patentee, and in the alternative that if the licence was exclusive, the accused test did not fall within the licenced field on the basis that the relevant technology was not licensed under the exclusive licence. Having considered the terms of the relevant agreement, Henry Carr J concluded that it was an exclusive licence which covered the relevant products.

In all this is an interesting judgment highlighting the multitude of different issues that can arise in relation to the enforcement of patents in this area.

¹⁵ [2004] UKHL 46
¹⁶ [2017] UKSC 48, see pages 7-8 in this publication for consideration of this judgment
¹⁷ [2002] EWHC Civ 1702
¹⁸ [2010] EWHC 1118 (Pat)



The UPC - an update



Alan Johnson
Partner

Almost exactly a year ago, after a few months' consideration post the Brexit referendum, the UK Government committed itself to continuing with its participation in the UPC project. To be honest that was quite a surprise, because the UPC is an EU project in all but name. But technically the UPC Agreement is a non-EU treaty and the UK gave an unconditional promise to ratify that treaty despite Brexit. In January 2017, the UPC Preparatory committee announced a start date of 1 December 2017. All was looking well politically for a few months with both the UK and Germany taking their steps toward ratification. But one German lawyer argued that the project was unconstitutional under German law, and on 31 March filed a complaint with the German Constitutional Court, the Bundesverfassungsgericht (BVerfG). The existence of the complaint remained unknown to the public until early June, but in the interim – in fact only a few days after receiving the complaint – the BVerfG rang the German President, President Steinmaier, and asked him not to sign the German ratification legislation whilst the court thought about the complaint. The President has done as he was told, and that is basically where we are today. The Court is still thinking about it and the President will not sign unless and until he is told he can.

What then, will happen next? One thing we know for certain is that the BVerfG has asked for amicus briefs from interested parties by the end of the year, but beyond that, in truth anything else is pure speculation. One possibility is that the German Constitutional Court will send the matter off to the CJEU to decide if the UPC is lawful under EU law. At one level that would be useful as it would give some certainty, but it would also mean a delay of at least another two years. If such a delay were not of itself fatal to the UPC, there would at least likely be a rather different political climate at that time, making any predictions as to the future of the UPC very difficult to make no matter what the CJEU might decide. Many German observers consider a reference to the CJEU rather unlikely, and indeed consider that the complaint has little substance despite its great length – but few, if any, of these commentators are actually *constitutional* lawyers as opposed to patent lawyers.

Hence, looking ahead, it is not easy to make any predictions. That said, there seems little chance that the UK will do anything other than ratify as it has committed itself to do, and being optimistic, the BVerfG could well dismiss the constitutional complaint in the early part of 2018, in which case it is realistic to think the UPC could start in late 2018, or at least before Brexit, including a provisional phase starting in summer 2018. One thing is for sure: for so long as the UPC remains a real possibility – and that certainly remains true – industry cannot afford to ignore it. At any one time, users are likely to have around eight months' – maybe a little more – warning of a start date, and accordingly should be ready to react within that sort of timescale.

For latest news on the UPC see: www.bristowsupc.com



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.

The competition law risks of responding to biosimilars entering the market



Sophie Lawrance
Partner



Matthew Hunt
Associate

To date, the competitive dynamics for biosimilars remain largely unexplored in competition case law. The very significant investments and clinical trials needed to launch a biosimilar product mean that the market dynamics are very different from generic equivalents to small molecule medicines. Indeed, biosimilars are often manufactured or marketed by major brand name companies, even if initially developed by smaller biotech companies. However, as recent developments demonstrate, the competition authorities are equally alive to conduct which deters, or reduces, entry by biosimilar products as they are for traditional generics.

Remicade is one of the first biologic drugs to face competition from biosimilars in the EU. It is the brand name for infliximab, produced by Merck Sharp & Dohme Limited ("MSD"). Infliximab is a chimeric monoclonal antibody used primarily in the treatment of patients with gastroenterology and rheumatology conditions such as Crohn's disease, ulcerative colitis and rheumatoid arthritis. In late 2013 two biosimilars to Remicade were granted regulatory approval in the EU, Inflectra, produced by Hospira (now owned by Pfizer) and Remsima, produced by Celltrion Healthcare. MSD's conduct at around the time these competing biosimilars were seeking to enter the market is now the subject of an investigation by the UK competition regulator, the Competition and Markets Authority ("CMA").

A CMA press release issued alongside a Statement of Objections that it sent to MSD in May 2017 indicates that MSD "broke competition law by abusing its dominant position through

a discount scheme for Remicade that was likely to restrict competition from 'biosimilar' versions of infliximab that were new to the market".

The investigation's focus on a 'discount scheme' is notable. The competition authorities have carried out a significant number of investigations into companies in the pharmaceutical sector in recent years, with infringement decisions in the area of 'reverse' patent settlement agreements, excessive pricing¹⁹, and a number of other on-going investigations in those areas²⁰. However, the use of discount schemes in the pharmaceutical sector has seen less enforcement activity to date²¹, nor has there been an investigation so heavily centred on biologic / biosimilar drugs.

MSD issued a public statement in response to the CMA's accusation, claiming that the "discounts in question meant that infliximab was competitively priced and offered savings to the UK National Health Service, without hindering competition".

This raises one of the most challenging issues faced by competition regulators when dealing with discount schemes, or other forms of rebates. On first consideration, it can appear counterintuitive that a practice resulting in a lower price for the purchaser could infringe competition law. This is especially true in the current political climate where the purchaser is the NHS, a body under intense pressure to make cost savings. However, the CMA will be seeking to put together a case showing that prices for infliximab would have been even lower but for MSD's conduct, and/or that the lower prices were designed to put MSD's competitors out of business. Indeed, the true focus of this case is likely to be on the total or partial foreclosure of the biosimilar competitor products. Following the recent *Intel* judgment of the Court of Justice, the CMA will have to demonstrate that MSD's discounts were sufficient to exclude equally efficient competitors²².

The CMA's investigation into MSD shows that pharmaceutical companies need to be aware that similar kinds of competition issues that affect generics may also affect biosimilars, despite the rather different competitive dynamics. Competition authorities are increasingly adopting narrow market definitions in the pharmaceutical sector. They often analyse markets at the ATC4 or ATC5 level, or even conclude that individual brands of molecules are in their own market. This means that there is an increased risk of companies being found dominant, and therefore at risk of infringing Article 102 TFEU if they implement an anti-competitive strategy to reduce the competitive threat posed by would-be entrants to the market, such as new biosimilar products.

¹⁹ For example, the Italian Market Competition Authority's decision in *Aspen*, and the CMA's decision in *Case CE/9742-13 Pfizer & Flynn*.

²⁰ For example, the Commission is also investigating *Aspen* for excessive pricing (*Case 40394*), and the CMA is investigating *Actavis* for excessive pricing and a potential pay-for-delay agreement with *Concordia*. For a full round-up of the recent UK cases, see [here](#).

²¹ The CMA did start an investigation into a suspected loyalty-inducing discount scheme in 2014 (*Case CE-9855-14*), however this was closed in June 2015 on grounds of administrative priority.

²² *Case C-413/14P Intel v. Commission*.

Competition

Biosimilars: NHS approach to procurement



Noel Watson-Doig
Associate

The financial pressures on the NHS have resulted in some questionable strategies in the use of framework contracts to procure biosimilar medicines.

The NHS's Commercial Medicines Unit ("CMU") has been known to use the (usually small) differences between biosimilars and the original product to extract the lowest possible prices from pharma companies by artificially distinguishing between products, through the use of exclusive procurement frameworks.

According to the European Medicines Agency's guidance on biosimilars, the active substance of a biosimilar and its reference medicine is essentially the same, though there will be differences due to their complex nature and production methods, resulting from their manufacture by living organisms rather than traditional chemical synthesis.

Despite this guidance, the CMU has used the existence of these differences to justify procuring new, exclusive, frameworks for different biosimilars as they receive marketing authorisation, despite having in place existing frameworks which could have been reopened. Equally, the Invitation to Offer for the new frameworks have specified that only the new biosimilar manufacturer is eligible to bid.

There is nothing unlawful about public authorities employing parallel procurement frameworks for similar products. However, there are serious legal concerns with arbitrarily limiting the companies eligible to bid on a framework by excluding certain players from the competition.

These legal concerns are compounded by the risk that in small markets, such as for biosimilar medicines, information in relation to prices on the earlier frameworks are likely to be relatively easy to obtain. As a consequence, the sole bidder for the new framework will be well placed to undercut its rivals on the earlier procurement, while those rivals are precluded from bidding in the new procurement process.

If the new bidder does win with an undercutting approach, those who won the initial framework are likely to find it impossible to compete with the lower priced products for some or all of the potential demand that they had originally hoped to supply, as they are contractually locked into the price they bid on the original framework.

In effect, the existing framework will be rendered redundant, the original bidders' access to the NHS purchasing market will be restricted, and the new biosimilar bidder will have secured a competitive advantage and privileged market position.

If a company is excluded from a procurement process for reasons that appear spurious and likely to affect its market position, it is important to challenge the CMU's decision-making process as soon as possible during the 10 day 'standstill period'.

The 'standstill period' is engaged after the winning bid has been selected and prevents the public authority (in this case the CMU)

from entering into the framework agreement, or contract, for ten working days in order to provide an opportunity to challenge the contract award.

Tactically it is also important that work starts on a potential claim in the High Court, as our experience is that the CMU is more likely to reconsider its approach if it is likely to have to defend its procurement decision in court.

A procurement challenge can only be brought for up to 30 days from the point when the claimant knew or ought to have known that grounds for starting proceedings had arisen. Once a claim is issued the procurement process is automatically stayed, although public authorities are usually successful in requesting that the stay is lifted.

The operation of such biosimilar framework contracts could also have significant implications for the ability of manufacturers of originator biologics to obtain interim injunctive relief against biosimilar market entry. The question of irreparable harm in a biologic/biosimilar situation has not to date been tested before the Courts in an interim injunction application, but one argument that might be used against the grant of an interim injunction is the slow uptake of biosimilar products, at least in comparison to generic small molecule pharmaceutical products. However, if these biosimilar procurement frameworks are able to accelerate biosimilar market entry, it may tip the balance in favour of applicants for interim injunctive relief in the biologics sector.

Merger control as a means of protecting and promoting innovation in the life sciences sector



Stephen Smith
Partner



Francion Brooks
Associate

When assessing proposed mergers and acquisitions between competitors or potential competitors (i.e. 'horizontal' mergers) for compatibility with the common market under the EU Merger Regulation, the European Commission has traditionally focused on the potential for effects on price and output. In other words, the focus has been to consider the potential loss of competition (and hence scope for increased prices) that might arise by the removal of one competitor from the set of companies offering competing products in the market.

More recent decisions have, however, seen the European Commission also focus on whether the transaction might undermine innovation. Given the nature of the industry, many of these decisions have related to acquisitions in the life sciences sector. In these cases, the Commission has concluded that where overlaps exist between the merging parties (either between pipeline products, or between pipeline and marketed products), there could be an impact on long-term innovation, as well as competition in existing and future drug markets. In short, the concern is that the transaction would result in the elimination of a credible competitor and the consequent abandonment of parallel

R&D programmes and/or reduction of investment in late-stage clinical trials.

In most of these cases, the parties agreed to make a divestment to allay these concerns:

- a promising late-stage pipeline product was divested to obtain approval of the acquisition of medical device company Covidien by Medtronic in 2014;
- two Novartis cancer treatments were divested to obtain approval of the acquisition of GSK's oncology business in 2015;
- certain sterile injectable drugs were divested to obtain approval of the acquisition of Hospira by Pfizer in 2015; and
- a number of assets were divested to obtain approval of the acquisition of Allergan Generics by Teva in 2016.

Most recently, in June of this year, the Commission approved the acquisition of Actelion by Johnson & Johnson subject to conditions ensuring that the clinical development of their innovative insomnia drugs would not be adversely affected. In particular, the remedies limited Johnson & Johnson's strategic influence over the development of those drugs which were under active development.

The Commission's approach in developing this so-called innovation theory of harm is not without its critics. Whilst there may be credible concerns regarding overlaps in late stage pipeline products, these are much more difficult to establish when looking at drugs earlier in the development process. Indeed, success rates for early stage drugs are notoriously low, with perhaps only a third of drugs in Phase II likely to move to Phase III trials, where even then, ultimate success is not certain.

Despite this uncertainty, in a number of these cases the Commission has intervened in respect of early-stage pipeline products. For example, in *Novartis/GSK (Oncology)*, part of the Commission's competition concerns related to therapies in Phase I and II clinical trials. Some economists have also criticised the Commission's economic rationale for intervention – a less competitive market increases the post-innovation rewards for companies which may increase their incentives to engage in R&D in the first place.

The European Commission's recent decisions in merger cases clearly reflects its wider policy of promoting innovation within the European Union. When considering potential collaboration opportunities and/or acquisitions, companies in the life sciences sector should be alive to these policy considerations which could result in concerns and ultimately remedies, even where overlaps are limited to R&D programmes at very early stages.

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.

Science in architecture – the way forward



Teresa Edmund
Partner



Ewan Viney
Associate

Living architecture can excite and capture the imagination. Succinctly, 'living architecture' is about constructing buildings that possess some of the properties of living things, bringing scientific expertise and new technologies to the construction process. Some scientists claim that humanity's very survival depends upon the successful development of living architecture, on the basis that living buildings could absorb pollutants and carbon dioxide, and have the potential to offer better protection against natural disasters.

Buildings that can repair themselves and cities powered by micro-organisms – these are examples of the potential application of biology and biotechnology to the built environment. These so-called "living buildings" look to a future where individual buildings and eventually even neighbourhoods and cities, include living systems in their design and engineering and share some of the properties of those living systems to become dynamic, adaptive and increasingly sustainable.

Building practices and methods have historically been constrained and involve the use of materials which, in essence, have remained unchanged for centuries. Living buildings seek to replace this with something completely new. Humans have long looked to nature for aesthetic inspiration, but in the future it seems that humans will progressively need to look to nature for practical solutions. To use termite mounds as an example – these structures have intricate cooling systems inside. Could these designs be used to create new more eco-friendly ventilation systems within buildings? Energy from fossil fuels consumed in the construction and use of buildings accounts for approximately 50% of the UK's CO₂

Real Estate

emissions. The energy requirement to produce alternative materials derived from natural materials, for example to replace concrete and steel, is much lower and the materials created are also recyclable- twin objectives in meeting the challenge of carbon reduction.

Early commercial uptake in modernising buildings has focused upon smart environmental controls and data-connectivity tools which simplify the management and efficiency of large buildings. The focus of bio and future architecture is developing materials which are self-sustaining, and generate a monetary and/or ecological value.

The technology already exists to create many of these alternative materials, from structures created from lab grown bone and egg to self-cleaning paint based on the physical structures of the lotus leaf. Bricks capable of recycling wastewater and generating electricity are being developed by the University of the West of England. The idea is that the bricks, when fitted together will create what will be known as “bioreactor walls”. The smart bricks will be filled with microbial cells and algae which are designed to self-adapt to changing environmental conditions; for example the changing air quality in a building. Each brick will contain different microbial fuel cells, specifically chosen to clean water, reclaim phosphate, generate electricity and facilitate the production of new detergents. The ultimate goal is to create a situation where bioreactor walls can treat building waste products whilst at the same time generating enough electricity to sustain the buildings they are housed within.

Developers are already trialling bio-concretes, which are made from renewable resources rather than our finite supply of limestone. The bacteria blended into them act as a repairing agent by sealing cracks as they emerge. Protocells, a kind of oil droplet which can be chemically programmed, have been shown to be capable of creating limestone and, as such, could be used to repair the foundations of Venice. CO₂ respondent materials are another key focus. Membranes which are able to trap and distil the environment around them and produce useful materials from the harmful aspects of our environment will be helpful in mitigating the damage being caused.

These and similar ideas will take time and investment before they become part of our everyday world but the role of bioscience in future building practice will be vital. Inevitably this will give rise to legal considerations.

Licensing and IP

A building or part of a building that is created by a new process, be that mechanical or biological, might have utilised a process or material that has been protected by an intellectual property right. Will a producer or a consumer need an ongoing licence or similar right to utilise the specific protected properties of the building that they have purchased? Similarly, we already buy many products which will continue to “upgrade” over their lifetimes by way of operating systems. How will this work in relation to bio products which might involve organic growth and regeneration? What growth will the owner of a building be entitled to, and how will any disputes over these rights be resolved?

Regulation

Biological and ecological processes will no doubt attract a regulatory framework which will be vastly different from today's building regulations. If something can interact with its environment, can the producer guarantee that there won't be contamination or cross contamination of the environment or long term harm to human health? The architect Alberto Estevez has created bioluminescent lemon trees by implanting them with jelly fish cells. These could replace street and other forms of lighting but only if the producers can guarantee the genetic safety of the bioluminescent lemon tree. Going one step further, if a building is able to register that its occupants are becoming unwell, could it be classified as a medical device?

Servicing, Insurance and Liability

If we are designing materials with a product lifespan vastly in excess of materials in use now and with very different properties, purchasers and providers will need to be comfortable with changing warranty expectations and liability periods. In addition, living materials will have different servicing requirements from those we are familiar with at present. This will also naturally feed into insurance considerations where the need to quantify new types of risk will lead to uncertainty. What happens if a living building dies? Or worse, what happens if a living building misdiagnoses, malfunctions, or causes harm?

The future of buildings looks incredibly exciting, with the potential to satisfy even the wildest dreams of futurologists. Integrating architecture and biological systems to bring the properties of living things to inert objects is increasingly seen as the way to deliver sustainable cities of the future. As these innovations continue to develop the surrounding legal framework will need to keep pace!



Tax

Tax at Bristows

Our tax experts enable clients from multi-nationals to start-ups to minimise tax exposure and do business while complying with the UK's maze-like tax system. We offer advice on the full range of tax issues affecting corporates, including VAT, stamp duties and other specialist areas. Core areas of expertise include helping clients, both UK based and overseas, to structure corporate and commercial transactions.

Recent tax developments



Julia Cockroft
Senior Associate

Topical and current tax news stories have centred on tax avoidance and illegal state aid cases, most notably involving multinational technology groups such as Apple. By comparison to the wider technology sector, Biotech has fared relatively well in terms of negative tax press. As far as UK tax is concerned, HM Revenue and Customs (HMRC) seem to have an increased appetite (and budget) to litigate disputes.

Over recent years, the government's stated aim has been to position the UK as the G20 country with the lowest corporate tax rate (currently 19% but reducing to 17% by 2020). This reduction in the headline rate, confirmed in the recent Budget, is balanced by a restriction on the use of carried forward corporation tax losses and substantial limits on the amount of deductible interest expense for corporation tax purposes. The tax relief available to companies to reflect inflation will also cease to apply to gains accruing from 1 January 2018 onwards as a consequence of the Chancellor's recent announcement that indexation is to be abolished. Whilst these significant changes are not unique to the Biotech sector, they will have an impact on all businesses and there will clearly be 'winners' and 'losers' in terms of effective tax rates.

EIS

Start-up and early stage Biotech companies will no doubt welcome recent changes to HMRC's published guidance and the Autumn 2017 Budget announcements on the Enterprise Investment Scheme (EIS). 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. In 2015, as a consequence of a state aid review of the UK EIS regime, various changes were made to the rules, including the introduction of "knowledge intensive companies" (KICs), which many Biotech companies are likely to constitute. In recognition of the significant time and cost involved in the development and commercialisation of IP, some of the

restrictive EIS rules are more generous for KICs. The usual 7 year age limit requirement is extended to 10 years for KICs and the limit on the amount of 'risk finance' investment a company can raise in its lifetime is increased from £12 million to £20 million.

The EIS legislation is often prohibitively complex given the size and scale of companies that are intended to benefit from the regime. HMRC have recently published additional guidance on its interpretation of these complex rules, helpfully clarifying the multi-faceted KIC definition. Satisfying this definition is now even more beneficial following the Budget announcements that have doubled the annual amount an investor can invest in a KIC from £1 million to £2 million and the amount a KIC can raise annually from £5 million to £10 million.

Research and Development (R&D) tax credits

In the 2017 Spring Budget, the UK's R&D tax credit regime was held out as an effective and internationally competitive element of the government's support for innovation. The regime was further bolstered in the 2017 Autumn Budget when the R&D expenditure tax credit was increased from 11% to 12%. Recent changes have increased the certainty and simplicity around R&D tax claims and the government is clearly making efforts to increase awareness of R&D tax reliefs, particularly amongst SMEs. As part of this objective, HMRC has recently launched a new online platform bringing together guidance, materials and short videos designed to facilitate R&D tax relief claims. The Autumn Budget also announced a new Advanced Clearance Service that will be introduced to give businesses confidence to make R&D investment decisions.

It will be interesting to see whether the UK makes any further changes to its existing tax relief offering (particularly EIS, R&D tax credits and the Patent Box) following Brexit if EU state aid restrictions no longer apply. The UK may welcome the opportunity to relax certain requirements.



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.

CAR-T therapy: the current landscape



Laura Anderson
Partner



Harry Taylor
Trainee

Chimeric antigen receptor T cell (CAR-T) therapy is currently the hot topic in the pharma world. In this article, we look at the science behind CAR-T therapy, the main players in the dynamic CAR-T market, and the challenges those companies are facing.

CAR-T therapy involves treating patients with T cells (a type of white blood cell) that have been genetically engineered to express a chimeric antigen receptor on their cell surface membranes. This receptor allows the T cells to recognise cancer cells and trigger their lysis (disintegration). The receptor is introduced into T cells using retroviral vectors and is usually based on single-chain variable fragments derived from monoclonal antibodies. Essentially, CAR-T therapy harnesses the power of the human immune system to treat cancer.

There are two types of CAR-T therapy:

- **Autologous** therapies, which involve extracting normal T cells from each patient and genetically engineering those T cells to target the cancer; and
- **Allogeneic** therapies, which involve genetically engineering T cells obtained from donors who are not cancer patients and treating the patients with those donor T cells

Kymriah

In August 2017, Kymriah became the first CAR-T therapy to be authorised by the US Food and Drug Administration (FDA). It is also the first GM cell therapy that the FDA has approved.

Kymriah (the brand name for tisagenlecleucel) is an autologous CAR-T therapy developed by **Novartis** in collaboration with the University of Pennsylvania and the Cancer Immunotherapy Frontier Program at the Children's Hospital of Philadelphia. In one Kymriah trial involving 63 acute lymphoblastic leukaemia (ALL) patients, 83% of patients were free of the disease three months after treatment. ALL is a rapidly progressing form of white blood cell cancer.

Kite Pharma, acquired by **Gilead Sciences** in August 2017 for \$11.9 billion, was recently the second company to obtain FDA approval for a CAR-T therapy, with FDA approval in October 2017. Kite's therapy, Yescarta (the brand name for axicabtagene ciloleucel), has shown promise in lymphoma trials, and has, in part, been developed in conjunction with the National Cancer Institute of the US National Institutes of Health. In the pivotal trial, 72% of patients with certain types of B-cell lymphoma responded to therapy with 51% achieving complete remission eight months after treatment. B-cell lymphoma is a different type of cancer than the ALL that Novartis' Kymriah therapy treats, demonstrating the broad applicability of this new form of therapy.

Other players in the market

There are currently several hundred clinical trials being conducted for CAR-T therapies and a hotly contested international race to market is ongoing in the field.

There are a few key players who, in the main part, are developing technology which originated from different academic institutions based in the US and Europe. **Juno Therapeutics** has always been a front runner, listed on NASDAQ with a market capitalisation of approximately \$4.8 billion. In March 2017, Juno suffered a set-back as it terminated its CAR-T trial for JCAR015 following the death of five patients who suffered from cerebral edema as a result of the trial. However, Juno is currently trialling several other CAR-T therapies, including three targeted at B-lymphocyte antigen CD19 (which is highly expressed on B-cells in B-cell lymphomas). Juno is working with the Fred Hutchinson Cancer Research Center, the Memorial Sloan Kettering Cancer Center and the Seattle Children's Hospital to develop the CAR-T therapies with this target. It is hoped that these therapies will treat non-Hodgkin lymphoma and various forms of leukaemia. With each of Novartis, Juno and Kite, the close ties to academia are clearly apparent.

Autolus is a UK biotech company and the UK market leader in CAR-T therapy. The company is developing CAR-T therapies for haematological and solid tumour cancers. Two such therapies, AUTO2 and AUTO3, act via 'dual targeting' mechanisms where the T cells are engineered to recognise two targets on the surfaces of cancer cells, rather than just a single target. These therapies are currently in dose-escalation Phase I/II trials, and trials for treatment of T cell lymphoma with AUTO4 are expected to start in the next six months. Bristows was pleased to advise UCL Business, a long-standing client, on the spin-out and initial £30 million equity financing of Autolus. Autolus subsequently completed a £40 million Series B financing and an \$80 million (£59 million) Series C financing in March 2016 and September 2017, respectively.

Challenges in the CAR-T field

Clinical trials

An ongoing issue with CAR-T trials has been the poor response levels among some patients. The absence of reliable pre-clinical CAR-T models means that the work is being conducted almost entirely in the clinic and it's difficult to predict outcomes. There is also a lack of reliable bio-markers; development of better bio-markers would allow more sophisticated prediction and monitoring of patient responses to CAR-T therapies, which would in turn increase the speed of bringing therapies to market. Also, with so many CAR-T trials ongoing, the industry is starting to express concerns about the ability to recruit patients in sufficient numbers – one commentator estimated that 160,000 patients are currently participating in CAR-T studies in the US.

Combinations

Low response rates among patients being treated with CAR-T therapies are starting to drive the industry towards combination therapies. One example is the combination of Kite Pharma's Yescarta (discussed above) with Tecentriq, Genentech's version of the immune checkpoint inhibitor anti-PD-L1. Anti-PD-L1 stimulates the patient's immune system by inhibiting the body's immune checkpoint response (a response which normally prevents the death of healthy cells by suppressing over-activity of the immune system).

A move towards these complex combinations is increasing the number of collaborations between industry players and these collaborations inevitably have to occur at an early stage in the therapy development process. Many such collaboration deals are, therefore, 'back-loaded' (with value contingent on clinical trial results and product sales) as a result of the speculative nature of current development activities.

The industry expects a vast pool of valuable data to become available as the first round of CAR-T trials comes to an end. The CAR-T players are already working on a raft of next generation products as the first CAR-T therapy is just entering the market. The available dataset should drive a better understanding of successful combinations and it is anticipated that this will in turn drive collaboration deal activity among the industry's key players.

Manufacture

Looking forward, the industry is wrestling with the complexities of setting up and operating a CAR-T business model, which will need to function "from bench to bedside". A particular challenge is, of course, the manufacture of autologous CAR-T therapies, given that autologous therapies require the extraction and genetic modification of patient T cells. Developing commercial manufacturing processes that are standardised is far from straightforward and a whole new business model is needed. The CAR-T leaders are planning for the future and have been investing in manufacturing capability. It's been fascinating to watch the approach of the industry, which has been to back the science and adopt the attitude of "if you build it, they will come".

Allogeneic CAR-T therapies would present less manufacturing complexity and cost, given that such therapies do not require the extraction of T cells from individual cancer patients and so could be manufactured in fewer production centres. The development of allogeneic therapies is following behind autologous CAR-Ts,

with French company **Collectis** currently developing a gene-edited allogeneic CD-19 CAR-T (known as UCART19), working in collaboration with **Servier** and **Pfizer**.

Pricing structures

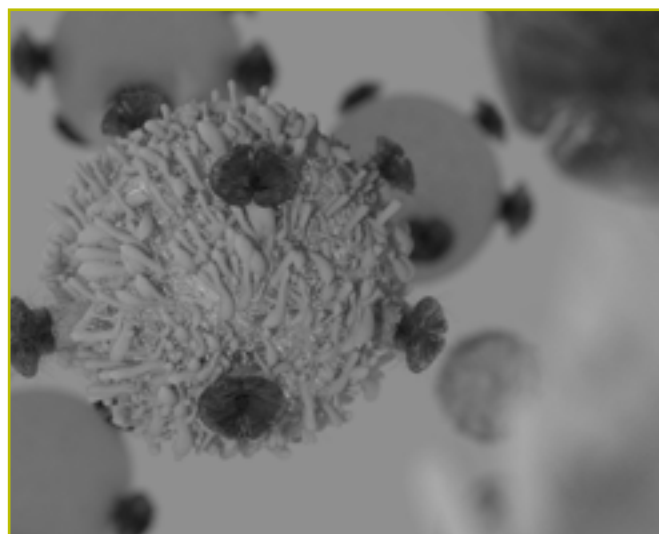
CAR-T therapies are expensive to develop, to produce and to deliver to patients, and concerns have been raised as to whether these therapies will be affordable. However, the industry appears confident that a viable financial model can be developed and that payers will support true cures. As far as combinatorial therapies are concerned, commentators are speculating that a pricing strategy will emerge in the same way that pricing structures for combinations of HIV drugs were established.

"Outcome-based" pricing has been much discussed and Novartis has already agreed a "pay-for-performance" pricing structure for Kymriah with the American Centers for Medicare and Medicaid Services (CMS). This is the first pay-for-performance agreement that CMS has entered into, and similar agreements are expected to be reached with private insurers. Under the Novartis-CMS agreement, Novartis will not charge for the therapy if patients do not respond to treatment within one month.

Use of such outcome-based pricing structures clearly adds contractual complexity for the industry, particularly with respect to determining whether or not a given patient has "responded" to treatment. In some cases, rebates can be offered based on whether or not a treatment reduces patient hospitalisations. Again, new financial models, industry norms and contractual structures will gradually be established as CAR-T products develop their own market.

Conclusion

We are currently witnessing a huge international experiment as the different industry players explore this powerful CAR-T technology. With the approval of Novartis' Kymriah and Kite's Yescarta, the potential is now being realised and the race to develop and launch CAR-T therapies heats up. Both the competitive landscape and the business model are developing rapidly. Patients' lives will be saved by this technology and the excitement in the industry is palpable.



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, neuroscience and veterinary medicine in the clinical setting.

The Advanced Therapies Manufacturing Action Plan – retaining and attracting advanced therapies manufacture in the UK



Hilary Jones
Of Counsel

It is well acknowledged that advanced therapies (cell, gene and tissue products and associated technologies) have huge potential for addressing unmet medical need and the long-term management (or even cure) of disease. The UK has established a strong lead in relation to research in advanced therapies which can be attributed to the global reputation of its universities and research institutes, its research infrastructure, together with the support provided by Government (including £54 million in grants supporting 126 projects over the last seven years) and the progressive approach of the MHRA towards certain regulatory issues. Additionally the Cell and Gene Therapy Catapult was set up to support academia and industry “to translate research into commercially viable products”. Although it is generally considered that the NHS has to date been slow to capitalise on the UK’s research strength, the activities of the National Institute for Health Research are now aiming to establish the NHS as an internationally recognised centre of research excellence²³.

The Advanced Therapies Manufacturing Taskforce (the Taskforce) published its [action plan](#) setting out its recommendations to Government and the Industry in relation to the manufacturing of advanced therapies on 23 November 2016. The recommendations address how the UK can maintain the strong position it has developed in relation to advanced therapy medical research and capitalise on the opportunities relating to the manufacturing of advanced therapy medicinal products (ATMPs). The taskforce was set up in early 2016 as a collaboration between industry and Government and its membership comprises over eighty different entities including the MHRA, NICE, the Knowledge Transfer Network, the Cell and Gene Therapy Catapult and academia.

The challenge recognised and addressed by the Taskforce is how to ensure that Government and industry act to “translate the research into manufactured products”, focusing on manufacturing scale up and commercialisation, with the aim of securing the UK a position as a world class hub for advanced therapies

manufacturing. It is recognised that there is competition from other jurisdictions with similar aims including the US and Japan (and within the EU activities are ongoing in Germany, Italy, France and Spain), hence the Taskforce believes that its recommendations need to be implemented within the next two years. The action plan contains six recommended actions to secure the UK as a global hub for manufacturing and we have summarised these below.

Potential growth in the cell and gene therapy market

The action plan states the global cell and gene therapy market will be worth between £9 and £14 billion per year by 2025. The UK market is estimated to be 4% of this at £0.4 to £0.6 billion per year by 2025 (higher than its normal share for small molecules/biologics). In the UK there are presently at least 48 advanced therapy medicinal product (ATMP) developers, and by the end of 2015 over 1000 jobs had been created and over £400 million attracted in investment. There has also been over 50% growth in clinical trials in the UK since 2013.

The Taskforce’s recommendations

- (1) Strengthen and secure an internationally competitive fiscal landscape to attract investment.

The Taskforce recommends that the Government should consider: strengthening the R&D tax credit system by extending the definition of R&D to include advances in manufacturing beyond clinical manufacture; reintroducing capital allowances for manufacturing assets and GMP facilities for commercial manufacturing²⁴; and reducing the patent box rate below 10%. Additionally, SMEs should be given support to utilize the incentives available.

- (2) Target and capture internationally mobile investments through a proactive and simplified process of engagement.

The action plan recognises that more needs to be done to maximise significant overseas investment whilst also giving UK companies appropriate attention and support. The Taskforce therefore recommends that Government calls for companies to come forward with their investment plans, and that the Government sets a mechanism to provide a single entry point for companies who are looking to invest. In addition the Department for International Trade’s Life Sciences Organisation is recommended to recruit a manufacturing specialist to support overseas and UK based investors and industry is recommended to provide business ambassadors to support the LSO’s efforts.

- (3) Maintain science and innovation funding to support industry developing cutting-edge technologies.

The Taskforce recommends that the UK should seek to capture £350 million in investment into advanced therapies manufacturing by making available loan/grant funding in the range of £30 million per annum over three years. In particular the action plan recognises a need to invest in the viral vector manufacturing infrastructure capacity and capability, since this is in short supply with much of the need being sourced from overseas at present. In addition, academics should be supported to have viral vectors manufactured effectively and at appropriate cost.

It is recognised that entirely new systems for the manufacture and supply of advanced therapies need to be designed and developed and that there will be a challenge in creating the bespoke technologies and tools needed. This includes the scaling up of manufacturing automation, the management of complex supply chains and the development of IT systems and standards for the capture of data on treated patients regarding, for example, product efficacy and advanced analytics. The action plan is clear that the focus on funding needs to remain.

- (4) Set out an end-to-end talent management plan to secure the relevant skills for emerging manufacturing technologies.

The action plan states that a conservative estimate is that 400 – 600 additional skilled staff will be needed over the next two years. Manufacturing processes are currently small-scale and therefore underdeveloped, and the main growth is seen as being in relation to competent technicians or operators and specialised roles such as regulatory professionals and qualified persons. The action plan recommends that the UK nurtures its graduates to avoid skills shortages and ensures that mobility of talent remains, since without this there is a risk that the sector will lose out to overseas countries. With Brexit on the horizon this becomes of particular importance. The Taskforce also considers that industry should lead on creating an end-to-end talent plan for the sector and that seed funding of around £1.5 million be available from Government.

- (5) Clearly set out a swift, predictable and viable route to market for these innovative products and give industry confidence that the UK is a progressive global hub.

The Taskforce saw a key challenge to be addressed as the adoption and reimbursement of advanced therapies, and that having clarity of a viable route to market will be essential to anchor manufacturing investment in the UK. The Taskforce considers that the Accelerated Access Pathway should be piloted for certain advanced therapies to allow Government, companies and the NHS to develop “novel systems for assessment, commissioning and usage that can accelerate patient access”²⁵.

The Taskforce also considers that the UK needs to send a “very strong signal” of support for these therapies to give industry confidence but at the same recognises that real concerns remain around how these therapies will meet cost threshold criteria, given challenges around immature data and data uncertainty. This concern will surely have been exacerbated by the changes to NICE’s appraisal process for highly specialised technologies (HSTs) that has been implemented since the action plan was published²⁶. Considerations highlighted include the exploration of risk-sharing schemes (which allow the quantification and management of immature data) and also setting up a short term reimbursement fund for early procurement by the NHS. There is also a recommendation for the NHS to set up a national network of cell and gene therapy treatment centres (CGTTCs), with government funding, which will help with the development of the supply chain and also the data infrastructure required to collect long term patient data.

- (6) Develop a long-term regulatory strategy and plan for the MHRA to lead in global standards, supporting the scientific activities and international outreach of NIBSC²⁷.

The action plan acknowledges that there is an industry interest in a global regulator setting gold standards for both quality and

standards themselves and that the UK is well positioned to lead on this. The MHRA’s Innovation Office is the MHRA’s first point of call for regulatory queries for medicines, devices and bloods. In combination with the Human Tissue Authority, Human Fertilisation and Embryology Authority and the Health Research Authority, the MHRA has formed the Regulatory Advice Service for regenerative medicines called the ‘One Stop Shop’ which NICE is also due to join.

Recognising the clear need for novel manufacturing processes and supply chains, the Taskforce recommends that MHRA, NIBSC and the British Pharmacopoeia lead a series of stakeholder meetings to identify current gaps in advanced therapies standardisation, address different aspects of cell, gene and viral vector materials as well as their manufacturing processes and products.

Conclusion

The action plan is an extremely thorough analysis of the changes that are needed in order to secure the success of advanced therapies manufacturing in the UK and the recently published Life Sciences Industrial Strategy²⁸ report to Government endorses the recommendations in this action plan in full and states that the principles should also be applied to other life sciences manufacturing sectors.

The action plan recognises that the high costs of manufacturing together with the low patient numbers (when dealing with orphan and ultra-orphan conditions) and the costs of lengthy clinical development means that undertaking commercial investment in advanced therapies is highly risky. The ultimate success of the UK’s manufacturing strategy and of advanced therapies as a whole will depend on action and success across several different fronts, but the impact of market access issues on success as a whole should not be underestimated.

The report by its nature focuses on the manufacturing of advanced therapies, but from a regulatory perspective there are of course challenges which affect the development of these products, including the classification of novel therapies within the existing legislation and guidance²⁹ and the development of medical devices used in combination with advanced therapies (i.e. combined products).

The report does not focus on the potential impact of Brexit, but there are many aspects which could impact on the successful implementation of the action plan (including the regulatory environment within the EU (and the role of the UK), the freedom of movement of talent and the introduction of import / export tariffs between the UK and the EU). It is certainly a space to be watched with great interest.

²³ The NIHR is “committed to making research faster and easier for industry and other funders”. For example “The introduction of a 70 day bench-mark for enrolling the first patient into a trial by participating NHS Trusts will ultimately lead to faster translation of research into improved treatments, interventions and services for patients and means more studies are likely to be carried out in this country.”

²⁴ The removal of capital allowances for commercial manufacturing assets was seen to have a strong negative impact for the manufacturing of biopharmaceuticals.

²⁵ The government’s final Report on Accelerate Access Pathways was published in October 2016 and the government has stated that it “will now consider the proposals and respond more fully in due course, mindful of the need to ensure affordability.” However, there has been no announcement of a product being accepted for the Accelerate Access Pathway as yet.

²⁶ Since April 2017 to use the Quality Adjusted Life Year methodology for the appraisal of HSTs, with a threshold of between £100k and £300k per year, as well as the introduction of the NHS ‘budget cap’ of £20 million in any of the first three years of the product being reimbursed (the introduction of which was unsuccessfully challenged via judicial review by the ABPI).

²⁷ National Institute for Biological Standards and Control

²⁸ Chaired by Sir John Bell and published on 30 August 2017.

²⁹ For example a genome editing tool such as CRISPR-Cas9 does not fit easily within the existing legislation and guidelines.

Is there such a thing as substitution or interchangeability for biosimilars?



Marie Manley
Partner



Eleanor Denny
Associate

Biological medicinal products have rapidly become one of the fastest growing areas of medicine and for many conditions they offer a new and more effective form of treatment. It is therefore unsurprising that biosimilars, since they were first introduced onto the EU market in 2006 (when Sandoz got a marketing authorisation (MA) for Omnitrope), have become an important part of the treatment landscape. Biosimilars being inherently cheaper than the biological medicinal product are preferred by the payers of medicinal products and therefore their use is encouraged. Therefore, in many jurisdictions there is increasing financial pressure for healthcare professionals (HCPs) to prescribe biosimilars rather than the 'reference medicinal product'³⁰. However, this financial benefit must be carefully balanced against potential patient safety concerns.

This article briefly sets out what biosimilars are then discusses the concept of interchangeability and substitution. It then goes on to discuss the regulatory framework regarding interchangeability and substitution in different jurisdictions and the different factors influencing changes to this framework.

1. Key definitions

a. What is a biosimilar?

A biosimilar is a 'biological medicinal product'³¹ that is similar (but not identical) to another biological medicinal product that has obtained a marketing authorisation on the basis of a complete dossier (i.e. the "reference medicinal product").

Biosimilars benefit from a simplified procedure to obtain an MA, the legal basis for which is set out in Article 10(4) Directive 2001/83/EC (the "Medicinal Code"), which states "*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided...*". Therefore, biosimilars are not required to provide the full set of data to demonstrate their quality, safety and efficacy. Instead biosimilars must conduct comparability studies to demonstrate their 'biosimilarity' to the reference medicinal product. If the studies are conclusive then the biosimilar would be able to rely on the safety and efficacy data generated by the reference medicinal product in support of its own MA (as long as the periods of regulatory data protection and marketing protection have expired³²).

b. The concepts of 'interchangeability' and 'substitution' of biosimilars

The terms "interchangeability" and "substitution" are rather confusing and are not used consistently in scientific publications. They are not specifically defined in the EU pharmaceutical legislation, and both relate to the action of replacing one medicine for another; however the EU Commission³³ distinguishes the two practices as follows:

- **Interchangeability:** the medical practice of changing, on the initiative of a HCP or with their agreement, one prescribed medicine for another with the expectation that it will achieve the same clinical effect in a given clinical setting and in any patient; and
- **Substitution:** the practice of dispensing one medicine instead of another equivalent medicine at the pharmacy level without consulting the prescriber. This is common practice in relation to identical molecules (i.e. generics of each other).

We have adopted these definitions throughout this article, although it should be noted that these definitions are not standard as different countries may use different terms and/or definitions (e.g. the FDA in the US define interchangeability differently³⁴). At the time of writing, discussions are on-going to try to develop standardised terms that can be used in MedDRA (a highly specific standardised medical terminology used to facilitate sharing of regulatory information internationally, developed by the ICH) and so this should help to align the different systems.

2. Is interchangeability and/or substitution possible?

In order to grant an MA for a biosimilar the EMA will review extensive amounts of comparability data (e.g. analytical studies, in vitro and in vivo non-clinical studies and clinical studies) produced to establish similarity between the biosimilar and the reference medicinal product to ensure that the "previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar". However, this review does not include a recommendation regarding whether said biosimilar should be used interchangeably with its reference medicinal product.

Decisions regarding interchangeability and substitution of biosimilars are outside the EMA's remit; however, the EMA has stated in guidance that "*[i]t is possible to switch from a biological reference medicine to a biosimilar medicine and this is a growing practice in some Member States. Any decision on switching should be taken by your doctor in consultation with you, and taking into account any policies that your country might have regarding the use of biological medicines*³⁵." Therefore, it appears in principle that the EMA accepts the possibility of interchangeability but not substitution.

However, it is clear that Member States retain the discretionary power to legislate on the interchangeability and substitutability of biosimilars. Therefore, there is variation between different countries' legislative frameworks and this is discussed below.

a. Interchangeability

Concerns have been raised by some stakeholders about interchanging reference medicinal products and biosimilars. As stated above, while biosimilars must prove that the previously established quality, safety and efficacy of the reference medicinal product applies to them, interchangeability of a particular biosimilar with its reference medicinal product is not tested. Therefore, there are concerns that interchanging could impact patient health as switching to biosimilars could lead to different immunogenic reactions and side effects. There is evidence that changes in manufacturing process can lead to unexpected adverse events and so changes in manufacturing and/or presentation between the reference medicinal product and the biosimilar may be of concern. For example, as detailed in a paper by C L Bennett et al.³⁶ the formulation of the drug Eprex was changed and this led to increased immunogenicity in the form of pure red cell aplasia (PRCA). Another example was in the case of peginesatide, which was given to 20,000 patients in the US in dialysis centres and severe anaphylaxis occurred in 28 patients leading to 5 deaths (this was thought to be due to the addition of preservatives as preapproval trials used single-use vials without preservatives whereas post-approval patients were treated with multi-use vials with preservatives).

However, there is growing evidence of the safety of biosimilars. For example, a recent guide published by the EMA and European Commission³⁷ stated "*The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines*". Therefore, use of biosimilars instead of their counterpart reference medicinal product should not be seen as unsafe for patients.

There is also growing evidence of the safety of 'interchangeability', for example, in the position paper published by Fimea (the Finnish medical agency)³⁸ it was noted that immunogenicity was unlikely to occur due to the fact that biosimilars have comparable structures, the active substances have the same amino acid sequence and similar post-translational profile, and inferior quality (impure) biosimilars are not allowed. The paper goes on to give examples of switching between biological medicinal products that could help agencies to evaluate the risks involved in interchanging. For example, it has been shown that switching between two non-similar but related biological products has not led to higher immunogenicity. Fimea concluded that switches between biological products are common and usually not problematic (e.g. during hospital tenders), currently there is no evidence for adverse effects due to switching from a reference medicinal product to a biosimilar, the theoretical basis for such adverse effects is weak and the risk of adverse effects can be expected to be similar to the risk associated with changes in the manufacturing process of any biological product. Therefore, Fimea's position is that biosimilars are interchangeable with their reference medicinal product under the supervision of an HCP. This is in line with the position of the French regulatory authorities which have taken a relatively relaxed position on interchangeability. Indeed, in May 2016 a report was released stating that while the advice had previously been to not switch during the course of a treatment, this practice would no longer be excluded so long as the patient consents, there is adequate clinical monitoring and there is traceability.

While there is some variation between the different regulatory frameworks, due to the growing body of evidence regarding the safety of interchangeability, many Member States have taken the position that interchanging between a reference medicinal product and a biosimilar is acceptable if it is managed by the prescriber and patient, plus (in many cases) that it is monitored. For example, in the UK, interchangeability is allowed and NICE advice states that "*[t]he choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient*"³⁹. However, as the biosimilar and its reference medicinal product will have the same international non-proprietary name (INN) it is good practice for HCPs to use the brand name of the biological medicinal product when prescribing to ensure substitution does not occur. Prescribing by brand name is also important for the purposes of traceability and pharmacovigilance.

b. Substitution

As stated above, substitution occurs at a pharmacy level without the intervention of an HCP. This practice is well established for traditional chemical medicinal products where generic medicinal products are identical to the reference medicinal product. Automatic substitution of generics is common as generics are almost always significantly cheaper than the reference medicinal products and substitution is both in the interest of the national health authorities (the 'payers') and the pharmacists who benefit from the difference between the purchase price of the generics and the reimbursement price of the INN.

The issue is that biosimilars are not identical to their reference medicinal product; they are 'similar'. Therefore, while there are potentially very significant cost savings in prescribing biosimilars rather than their reference medicinal products, Member States have traditionally been resistant to allowing substitution. These concerns are illustrated by the legal requirement provided in Article 102(e) of the Medicinal Code that all Member States must take appropriate measures to "*identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report*" to ensure a proper application of the principles of pharmacovigilance and traceability.

To date, Member States have taken diverging positions towards the substitution of biosimilars. For example, the UK and Spain do not permit automatic substitution of biosimilars at the pharmacy level. In contrast, in December 2016, France became the first EU country to pass a law to allow substitution of biological medicinal products by adopting the 2017 French Social Security Act (PLFSS). PLFSS allows for substitution of biosimilars for prescribed reference medicinal products both at the start of the course of medicine and during it. However, this is subject to the HCP prescribing the product not marking the prescription as "non-substitutable" and so substitution is to some extent controlled by HCPs.

It should be noted that while in principle this law is in force in France, in practice it is not possible to substitute biosimilars until a Decree has been passed that sets out the particulars of how substitution will work. As of 30th November 2017 a Decree regarding the relevant article of PLFSS has not been passed and so substitution is not currently practised in France. The delay in passing the Decree might reflect that there are still diverging views

on how to allow substitution and the challenges of ensuring a sufficiently robust pharmacovigilance system is in place in order to monitor and trace biosimilar products substituted for their respective reference medicinal products.

3. What does the future hold for biosimilars?

As biological medicinal products are a relatively new and ever increasingly important area of medicine the legislation surrounding their use will continue to develop as more data becomes available about their safety and efficacy. Healthcare payers are under ever increasing financial pressure to substitute / interchange biosimilars for their more expensive reference medicinal products, as this would not only reduce the cost of treatment but also increase patient access. Interchangeability is already widely accepted and used across the EU and there is an increasing amount of evidence indicating that this is not exposing patients to significant health risks. Despite these factors, Member States are still resistant to allowing substitution of biosimilars as there is insufficient evidence that it is safe and there are concerns about pharmacovigilance and traceability. Therefore, at this point in time, it seems that the economic benefit potentially enjoyed by 'society' does not outweigh the potential safety risks to 'individuals'.

However, it is our view that, as long as there is no major adverse incident relating to the use of biosimilars, and driven by financial considerations, it is likely that substitution of biosimilars in some form will become acceptable. As deciding the rules on substitution is a Member State's prerogative, all Member States will progress at different rates and may implement different systems. For example, some may decide there is sufficient evidence to use the same system as traditional generics (i.e. immediately becoming substitutable on authorisation) whereas others may implement a different system such as that substitution may be allowed on a case-by-case basis if sufficient evidence is available that switching between the reference medicinal product and biosimilar is not putting patients at risk (i.e. after X years of commercialisation).

³⁰ Defined in Article 10(2)(a) of the Medicinal Code

³¹ Defined in s3.2.1.1(b), Part I, Annex 1 of the Medicinal Code

³² See Article 10(1) and (2) of the Medicinal Code

³³ Consent Information Document available at <http://ec.europa.eu/DocsRoom/documents/8242>

³⁴ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm>

³⁵ https://ec.europa.eu/growth/content/information-patients-what-i-need-know-about-biosimilar-medicines-0_en

³⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404762/>

³⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (last updated April 2017)

³⁸ www.fimea.fi/documents/542809/838272/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf

³⁹ <https://www.nice.org.uk/advice/kit15/chapter/options-for-local-implementation>

Corporate

Corporate at Bristows

Our experienced lawyers advise on every aspect of corporate transactions, including tax, employment, UK and EU competition/anti-trust, regulatory, real estate, IT, data protection and IP issues. Our recognised expertise in IP and technology puts the firm in an exceptionally strong position to advise on corporate and financing transactions in various sectors including Life Sciences.

The lure of the US for UK biotech



Alex Evans
Associate

The UK has a world leading life sciences sector which is underpinned by an array of globally-recognised universities and research centres, and a nurturing environment for funding and growing start-ups.

Yet, although the UK is evidently committed to biotech companies in the early stages of their life cycle – as has been shown in a report by the UK BioIndustry Association (BIA Report)⁴⁰ – it has historically not been as successful as many would like in developing late-stage biotech companies. It is well-understood that the US equity markets are the destination of choice for biotech companies seeking to raise significant finance in order to grow and scale quickly. This was exemplified a few years ago when UK biotech companies were rushing to raise money on Nasdaq's booming biotech market (whether by direct listing or by way of a reverse ("fallen angel") merger) and take advantage of the wealth of eager and suitable investors. For example, in 2015, Adaptimmune Therapeutics and Summit Therapeutics listed on Nasdaq and raised approximately \$230m between them.

Moreover, Nasdaq offers UK biotech companies not only the opportunity to raise finance on an IPO, but the opportunity to return to the market for follow-on investment – for example, GW Pharmaceuticals has returned to Nasdaq four times and raised over £400m in follow-on funding since it listed on Nasdaq in 2013.

Despite the lure of the US, the LSE's junior market – AIM – has demonstrated in recent years that it can be an important platform for initial and follow-on financing. According to the BIA Report, six UK biotech companies raised a combined £99m by listing on AIM in 2016 and raised £862m in further issues, which, as the report states, is evidence of the UK market endeavouring to close the gap on Boston and San Francisco's pre-eminence.

So far, however, 2017 has been a quiet year for the LSE which reflects the (almost cyclical) cooling of the global biotech market more generally: when Destiny Pharma listed on AIM in September 2017 raising £15m it became only the second life sciences company to list on the LSE this year. Investor confidence in the



UK has undoubtedly been hampered further by uncertainty created by geo-political instability and Brexit. It therefore seems that, despite the UK capital markets showing promising signs, the trend of UK biotech companies looking to the US in pursuit of major financings will continue for the time being at least. By way of example, Bristows advised NuCana, an Edinburgh-based company, on the UK aspects of its recent listing on Nasdaq through which it raised approximately \$114m in order to fund late-phase trials of enhanced chemotherapies for resistant tumours.

40 <https://www.bioindustry.org/resource-listing/building-something-great-uk-s-global-bioscience-cluster.html>

Regenerative medicine sees investment growth in 2017



Sam Munday
Associate

The emerging field of regenerative medicine is seeing record levels of investment as investors seek to benefit from its wide-ranging medical applications. With the results of the first clinical trial based on induced pluripotent stem cells (iPSs) being published earlier this year, investors hope that the returns on such investments are reaching ever closer.

Why the interest in regenerative medicine?

Regenerative medicine includes many areas of research which attempt to develop methods to regrow, repair or replace damaged or diseased cells, organs or tissues, primarily through the use of stem cells. It is recognised that such technologies have the potential to treat an almost immeasurable number of diseases, from wet macular degeneration and Alzheimer's, to the growth of entire organs for transplantation.

UK funding

Regenerative medicine is in its relative infancy, but investment from government initiatives and institutional and angel investors is increasing. A report from Goldman Sachs released earlier this year indicates that venture capital investment totalled \$807m in 2016, an increase of \$511m since 2011⁴¹. In Q1 2017, a total of £128m was invested in the UK, with IP Group and Touchstone Innovations being the two largest players, each having invested in four companies. Unlike other B2C sectors, crowd funding has been relatively absent – SyndicateRoom is the only platform which has participated in more than one raise⁴².

Investments in the UK have typically been at the seed or venture stages of biotech companies (106 of the 107 investments)⁴². Such companies include Oxstem, a group spun-out from Oxford University, which develops cell programming therapies through a number of techniques, such as the delivery of small molecule therapeutics to activate innate repair mechanisms. In 2016, Oxstem received a total investment of £16.9m, fuelling five new spin-outs (from Oxstem) targeting different medical needs.

The UK Regenerative Medicine Platform

In 2013, the UK Regenerative Medicine Platform (UKRMP) was set up by the Medical Research Council, Engineering and Physical Sciences Research Council and Biotechnology and Biological Sciences Research Council to help realise the goal of accelerating scientific discoveries in regenerative therapies to clinical application. UKRMP has invested £25m across five 'hubs' which link experts in specific fields within the biological and physical sciences with engineers and clinicians across 20 UK universities. The Platform

has pledged a further £17m over the next five years to help build on its success. Applications for funding closed in July of this year, but it will be interesting to see in early 2018 how this money has been allocated and the new technological developments that will emerge as a result.

The UKRMP works closely with the Cell and Gene Therapy Catapult, an initiative which works with academia and industry in bringing forward important new technologies that can be industrialised and turned into advanced future medicines. Bristows has advised a number of biotech companies which have worked with the Catapult, including Azellon. This spin-out from the University of Bristol has developed a technology to help treat meniscal tears by inserting a membrane seeded with a patient's own mesenchymal stem cells, termed the Cell Bandage, into the damaged cartilage to aid tissue repair. At the end of last year, Azellon announced the results of an encouraging Phase I/IIa trial and is currently developing, in collaboration with the Catapult, an allogeneic version of the Cell Bandage which it hopes will help reduce costs and remove the need for two operations.

Japan leading the way

Following the discovery of iPSs by Shinya Yamanaka of Kyoto University in 2012, investment in Japanese biotech companies has flourished. This, together with its government's relaxation of approval regulations, makes Japan one of the world's fastest places to bring a regenerative product to market, with regenerated skin and cartilage already in use in Japanese patients⁴³. In April of this year, a Japanese group was the first to publish results from a Phase I clinical trial⁴⁴. Europe and the US are currently lagging behind, but by the close of this year, the FDA, EMA and the Japanese PMDA are expected to issue coordinated draft drug guidelines regarding the use of iPSs in pre-clinical trials which should help to fuel further research and bring these technologies to market⁴³.

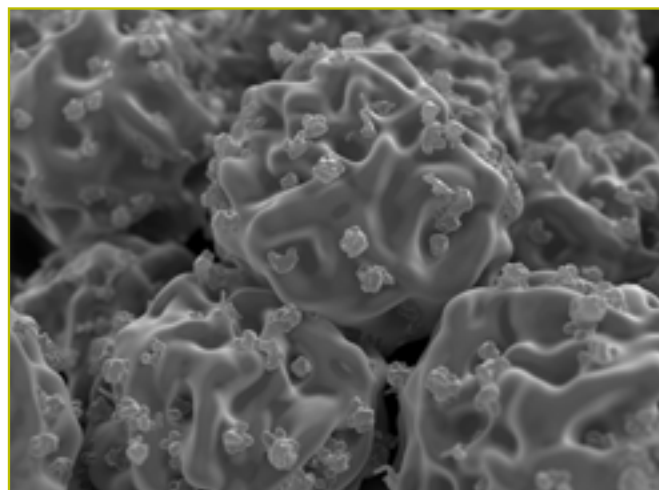
The global regenerative medicine market is set to reach \$120bn by 2030 which will be welcome news for investors⁴³. As research into regenerative medicine intensifies, opportunities for outside investors looking to take advantage of this emerging technology will follow. Once authorisations are granted in Europe and the US, investors hope that these potentially life-changing treatments could yield extraordinary returns.

41 <http://uk.businessinsider.com/venture-capital-interest-in-regenerative-medicine-2017-4>

42 <http://goo.gl/P4mkXX>

43 <https://www.bloomberg.com/news/features/2016-06-27/stem-cell-crusader-sparks-new-hope-for-fighting-diabetes-heart-disease>

44 Mandal, M. et al. (2017). Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. *N Engl J Med*, 376, pp. 1038-1046



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 “Genomic Dream”



Adrian Sim
Partner



Robert Vile
Trainee

Earlier this year, the UK’s Chief Medical Officer announced it was time to realise “the genomic dream”⁴⁵. Over the last 15 years, the timeframe and cost of sequencing a human genome have been dramatically reduced, opening up new possibilities for genomics – the study of genomes – and for personalised medicine.

Large groups of patients with similar symptoms can now be separated out into more specific groupings by using their genetic sequences. Specific variations in an individual’s genome can signpost the effectiveness of particular medicines and their side effects, along with the cause of the disease, what stage it is at, and risk of future disease. Last year these techniques allowed the Wellcome Trust Sanger Institute to determine that the most common form of leukaemia is in fact not one disease, but eleven distinct diseases, each with specific requirements for treatment.

The 100,000 Genomes Project

These advances in genomics have allowed researchers in the industry to set ambitious targets. Genomics England is leading the genomics revolution with a project to sequence and annotate the genomes of 100,000 NHS patients. The aim of the ‘100,000 Genomes Project’ is to bring benefits to patients by creating an ethical and transparent programme which will form the basis of a world-leading genomic medicine service for the NHS. In order to tackle a project of this magnitude, Genomics England has had to navigate a complex web of arrangements with its sequencing partner Illumina, its network of Genomic Medicine Centres, secure data centre, annotation and interpretation providers.

Data Storage and Privacy

While the legal and regulatory issues surrounding this ambitious project are many, it is the petabytes of data generated by the project that pose the greatest challenge. Under the General Data Protection Regulation (‘GDPR’)⁴⁶, which will apply from May 2018,

genetic data will be classified as a ‘special category of personal data’. As such, it will be subject to more stringent conditions of processing (e.g. meaning any consents must be “explicit”), trigger mandatory data protection impact assessments and for organisations processing a significant amount of genetic data, the appointment of a data protection officer.

Anonymisation of such data is often used as a way to safeguard privacy. However, it has been found that in certain circumstances genetic research participants can be identified from ‘anonymous’ data, either by cross-referencing their data with publicly available information, or by matching their data to a sample of their own DNA⁴⁷. So, the coming years are likely to see a challenge as to whether “anonymization of whole genome sequences” is an inherent contradiction. This could have a significant impact on the genomic industry and also the bases on which clinical trials are run.

IP, Crowd Sourcing and Commercialisation

Although the UK government continues to fund advances in genomic medicine, collaboration with industry and the academic research community is assuming growing importance. One way in which Genomics England has engaged with the broader scientific community is by creating PanelApp⁴⁸, a crowdsourcing tool which allows gene panels to be shared and evaluated by experts around the world. This is just one building block in a growing interest from researchers in carrying out analysis across “federated datasets” – the ability to search and interpret genomic data not within a single dataset, but via a single point of access across an array of worldwide datasets. A federated approach raises significant commercial, technical, privacy and IP challenges that have yet to be resolved.

Looking Ahead

The UK is well positioned to be at the forefront of the gene sequencing and personalised medicine industry and by the end of 2019, the government hopes to have developed a genomic medicine service for the NHS in England. As the world gets closer to realising the genomic dream, organisations like Genomics England and the 100,000 Genomes Project will have to continue navigating the complex legal and regulatory landscape which has formed at the confluence of science, technology, IT systems, IP and data protection.

⁴⁵ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/631043/CMO_annual_report_generation_genome.pdf

⁴⁶ Our EU GDPR 10 things you need to know note is available at <https://www.bristows.com/news-and-publications/articles/the-eu-gdpr-10-things-you-need-to-know/>

⁴⁷ <http://www.nature.com/news/privacy-protections-the-genome-hacker-1.12940>

⁴⁸ <https://panelapp.extge.co.uk/crowdsourcing/PanelApp/>

Secondary1st

We at Bristows LLP are proud to provide our continued support to Secondary1st, a charity founded in honour of our friend and colleague, Rosie Choueka.

The charity's aims are to raise awareness of secondary breast cancer and to raise funds to assist research into seeking a cure for the disease.

A year on...

In October 2017, just over a year after the charity's launch, members of the Bristows Charities committee alongside fellow member, Bristows partner and Secondary1st trustee, Pat Treacy, were proud to attend the presentation of Secondary1st's first grant to fund research into secondary breast cancer.

This grant has allowed the appointment of the very first "Secondary 1st Researcher", Michaela Lesjak, who will be working on a project led by Dr Claire Wells (Leader of the Cancer Cell Invasion and Metastasis Group at King's College London) in collaboration with Professor Tutt. Professor Tutt is Head of the Division of Breast Cancer Research and Director of the Breast Cancer Now Research Centre at the Institute of Cancer Research, and Professor of Oncology and Director of the Breast Cancer Now Research Unit at King's College London. Within Dr Wells' team, Dr Michaela Lesjak will conduct research exclusively into secondary breast cancer.

The presentation of the grant took place at the Breast Cancer Now Research Unit at Guy's Hospital, King's College London. The event was an occasion for the friends and family of Rosie Choueka and Secondary1st trustees, patrons, members and friends to gather together to reflect on the purpose and progress of Secondary1st since its launch in July 2016.

This was a truly remarkable and emotional occasion, with Rosie Choueka's family warmly thanking all the supporters of the charity and explaining the difference it has made to Rosie's family and the wider community.

The audience had the opportunity to hear from Baroness Morgan of Breast Cancer Now, who have partnered up with Secondary1st to assist the charity to fulfil its mission, and also from Professor Tutt who described the need "to understand how the process of metastasis hijacks normal biology" in order to "change the outlook for secondary breast cancer patients". Professor Tutt then introduced Dr Wells and her post-doctoral researcher, Dr Lesjak.

This team is investigating how cancer cells can dissociate from the primary tumour, invade the surrounding tissue and then metastasise to other organs, with particular reference to two molecules, PAK4 and RhoU, which work together to make cancer cells more invasive. By understanding the role of these two molecules in the spread of cancer cells around the body, the team can start to work out how to develop new treatments to stop this spread.

Secondary1st has raised over £160,000 since its inception, £75,000 of which has been included in the grant which was presented to Dr Wells in order to fund Dr Lesjak as her post-doctoral fellow. This grant of £75,000 is in line with the charitable objectives of Secondary1st and also picks up on Rosie Choueka's connection with Kings College London, where she did a post-graduate course.

The cheque was presented by one of the charity's patrons, Dr Who, Peter Capaldi.



To learn more about Secondary1st or to donate, please visit their website

www.secondary1st.org.uk

Secondary1st
Seeking a cure for
secondary breast cancer

Movember

The Movember Foundation is the only global charity focused solely on men's health.

Gender is one of the strongest predictors of health around the world: men die on average six years earlier than women; three out of four suicides are men; and prostate cancer takes the lives of 380,000 men each year.

Movember exists to stop men dying too young, and to help them live happier, healthier, longer lives.

Over the past 13 years, over 5 million supporters from around the world have joined Movember's men's health movement and raised funds for men's health. These funds have been invested in more than 1,200 projects that focus on the following key areas: prostate cancer, testicular cancer, mental health, and suicide prevention.

In the UK, one of the charity's most significant investments is the establishment of two Movember Centres of Excellence. These are hubs for researchers to jointly tackle some of the biggest challenges in prostate cancer. The Manchester-Belfast Centre is exploring the biology of high-risk prostate cancer, and cancers that are likely to relapse after initial radiation treatment. This work is helping to develop precision medicine approaches for the use of radiation and DNA-damage therapies in locally advanced and metastatic prostate cancer. Already, researchers at the Manchester-Belfast centre have developed tests to identify localized prostate cancer that is at risk of spreading beyond the prostate, as well as men whose cancer is unlikely to respond to radiotherapy. This work is advancing the boundaries of what is known about different forms of prostate cancer, as well as how treatments can be tailored to the individual needs of each man.

One of the most recent discoveries at the Belfast-Manchester Movember Centre of Excellence is the identification of a 'metastatic signature' in the genetic code of some prostate cancer cells which could help identify which cancers are aggressive and which are harmless.

The researchers looked at the genes expressed by primary prostate cancers, primary prostate cancers with known metastases, metastatic lymph node samples, and prostate tissue that they knew had no cancer within it. They found a cluster of

70 genes that were expressed the same in all the metastatic lymph node samples, all of the primary prostate cancers with known metastasis and some of the primary prostate cancer samples. Importantly, this gene expression pattern – or 'metastatic signature' – wasn't shared by any of the normal tissue or the rest of the primary prostate cancer samples.

They then needed to confirm if these results really could predict which men were at risk of developing metastatic prostate cancer. So they tested their metastatic signature against publicly available sets of prostate biopsy samples, matched to clinical outcome. These tests confirmed that the metastatic signature could successfully identify primary prostate cancers that would eventually spread beyond the prostate.

Aiming to end the biggest dilemma facing men at diagnosis

This is an important development, because the question 'to treat or not to treat' is still a big dilemma facing men diagnosed with prostate cancer and their doctors.

The researchers working on this project hope that this test could eventually help doctors identify which men would be safe to recommend for active surveillance, as well as instantly identifying men who are at risk of cancer recurrence after prostate surgery and so should be offered more radical treatment straight away.

The work of the Movember Foundation simply wouldn't happen without the passion and support of men and women around the world who value the health of men and take action to improve it.

Bristows are proud supporters of Movember, who are also clients of the firm. We have acted as primary UK legal advisors and have advised on a number of confidential charity, tax and employment matters.

Last year, Bristows internally hosted a number of events in order to fundraise for Movember which resulted in us taking home the Legal Challenge Moustache trophy as well as coming 10th in the overall National Leaderboard. These events included learning the Dance of Zorba, Hula Hooping classes, hosting a Men's Health Seminar, Mo Running and a Man of Movember moustache competition. The picture below shows many of our fundraisers.



Q&A

Dev Kumar is the Head of Legal and Compliance for EUSA Pharma, a dynamic, global speciality pharmaceutical company committed to bringing innovative medicines to patients. Dev qualified as a medical doctor in the UK in 1998 and practised in Obstetrics and Gynaecology / IVF and Reproductive Medicine for several years before entering the legal profession. After graduating, he trained and worked at Bristows before moving in-house. His previous roles include legal and compliance positions at Boehringer Ingelheim and Biogen. Dev also has a BSc in Psychology, an LL.M in Medical Law and an MA in International Policy and Diplomacy

All views and opinions expressed in this article are personal to Dev Kumar and do not necessarily reflect those of EUSA Pharma.



What scientific biotech developments do you expect will take centre stage in the next 5 and 10 years?

Nanotechnology interests me and I expect to see increasing use of nanotechnology in the biotechnology and pharma industries at all stages of development. From formulations for delivery optimisation to imaging and diagnostic applications in clinical trials, nanobiotechnology has the potential to greatly assist how we diagnose, treat, and prevent disease. We have already benefitted from great advances in gene therapy and the possible interaction between the two technologies brings about potential for more focussed drug-delivery / receptor targeting to elicit the required efficacy and response, while minimising side effects.

How long have you worked at EUSA Pharma for and what does your role involve?

Although I've only been at EUSA Pharma for five months it has been an incredibly busy and exciting few months. The role involves overseeing the legal and compliance affairs of the company globally, coordinating all aspects that one would typically associate with a General Counsel position: managing the IP portfolio, dealing with litigation, assisting on business development opportunities and balancing the commercial needs of the company with an ever increasing and complex regulatory and compliance environment. It is a very hands-on job, however; whilst you will undoubtedly provide legal and compliance advice, the expectation is that as part of the senior management team, you're an integral part of the business and focussed on driving the company to achieve its objectives and making a wider contribution in general.

What have been the highlights of your current role?

Although my career at EUSA has been relatively short, during that time I've seen two oncology drugs approved by the European Commission, which is remarkable for a company the size of EUSA, and when you consider that our story is relatively young to the extent that the company was launched in 2015. It has been an astonishing success story so far, but there is still much more work to be done to ensure that patients can access innovative and effective treatments. Nonetheless, getting involved in the strategic direction that the company pursues as it grows is tremendously fulfilling. I also have the fortune to work with some exceptionally talented and motivated individuals throughout the company and, closer to home, within the legal and compliance team. Working with such a gifted group of individuals is a real inspiration for me and keeps me on my toes and constantly learning.

What is the most difficult thing about your job?

There are lots of difficulties that we face as an industry and as a company. However, the most challenging part of the job is maintaining the culture of the company as we continue to grow and expand our footprint. Change can bring uncertainty and can prove disruptive for a business. Whilst some people view change as an opportunity, others find the uncertainty unsettling. Whilst I tend to fall into the former category and am relatively comfortable with change, it's important to recognise that people will deal with change differently and with different rates of acceptance and commitment. Communication is therefore important, especially when your organisation is facing change, and keeping people informed can help them to see the bigger picture and reduce anxiety.

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

Editorial Team



Dr Robert Burrows

Partner

robert.burrows@bristows.com

Robert advises on patent and other IP litigation matters in the UK, particularly for clients within the life sciences sector. Many of the cases he has managed in recent years have required the coordination of parallel proceedings in multiple jurisdictions within Europe and elsewhere in the world.



Dr Gregory Bacon

Partner

gregory.bacon@bristows.com

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

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