BIOTECH REVIEW

ISSUE 4

Index

Introduction

Dear Readers,

What a year it's been. On the political front we've had the double whammy of the UK Referendum and US Presidential election results. With regard to the latter, we now know that the future is orange, but in keeping with an old telecom company's slogan, is it still bright? We think it is.

Yes, we live in uncertain times, but they are also exciting times. In the remainder of this publication, we seek to shine a light on some of the more important developments in and issues facing the Biotech sector.

The Review therefore includes the latest on topics such as plausibility, which continues to play a major role in the validity of Biotech patents. We also look into matters such as securing funding for Biotech projects, regulatory issues for Biosimilars and, with the continued uncertainty regarding Brexit, we include a special feature on the possible economic models that could be adopted and their potential impact on your business.

As with all our publications, we welcome any feedback you might have and would be delighted to provide you with more information on any of the articles featured in this Review.

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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.

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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.

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Brexit

Brexit: What impact will it have on the biotech sector?

The full effect of the UK's vote to leave the European Union will certainly take time to materialize. It is still yet unclear whether the UK's exit from the EU will be "hard" or "soft" (or indeed happen at all). However, growing concerns within the biotech community are already palpable and the questions are many.

Will the UK biotech and scientific community be protected? Will pharma and biotech start relocating to EU jurisdictions? What will happen to access to capital if banks start leaving the UK? How will the UK replace the significant flow of funding from the EU? How will IP rights be protected and defended in the UK and Europe? What happens to the talent pool (scientists and employees) if free movement of people is threatened?

In this section, we outline some of the different options available to the UK post-Brexit in terms of its international trading arrangements and some of the impacts that these could have on the biotech sector in the UK.

Brexit

$25b in revenue generated by European biotechs in 2015

(Source: EY Biotechnology Report 2016)

Almost **US$10b** in capital raised by European biotechs in 2015.

UK was the leader for innovation capital:
$2.4b total funding
$884m venture funding
87 investments made

(Source: EY Biotechnology Report 2016)

2,259 biotech companies in Europe and over **72,000** employees

(Source: EY Biotechnology Report 2016)

1,045 biotech companies in UK

(Source: UK Biotech Database)

UK is one of the largest recipients of research funding in the EU

(Source: UK EU Life Sciences Transition Programme Report – UK EU Life Sciences Steering Committee)

UK is European HQ location of choice for over a dozen global pharma/biotech companies

(Source: UK EU Life Sciences Transition Programme Report – UK EU Life Sciences Steering Committee)

Different Brexit Models

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In the immediate aftermath of the Referendum vote on 23 June 2016, five different Brexit models (or variations thereof) were cited as options open to the Government for the UK's future trading position with Europe and globally. These were:

1. Leave the European Union (EU), but remain a member of the European Economic Area (EEA) (often referred to as the 'Norwegian model');

2. Leave the EU, re-join the European Free Trade Association (EFTA), but stay outside the EEA (often referred to as the 'Swiss model');

3. Leave the EU, but join an EU customs union (often referred to as the 'Turkish model');

4. Leave the EU, but negotiate individual trade terms to retain at least some access to the single market (often referred to as the 'Canadian model'); or

5. Leave the EU and fall back on World Trade Organization (WTO) trade terms.

Over the past few months the debate has evolved, with various statements made from representatives both of the UK Government and key EU leaders. At this stage there is still a great degree of uncertainty concerning what the likely ultimate destination for the UK will be. On the one hand, the UK Government (or at least the UK Prime Minister) has made statements that lean towards a bespoke 'Canadian model' for the UK, protecting the UK's access to the single market whilst retaining a degree of control over immigration. But on the other, there have been numerous statements from a variety of EU leaders making clear that access to the single market is inextricably linked with the four freedoms, including free movement of persons.

In addition, a hardening of the view that if the UK voted for anything on 23 June, it was the reassertion of control over immigration, renders it difficult to see how the Government could sell the Norwegian model as an acceptable political outcome. Indeed, Theresa May herself has suggested on numerous occasions that the UK would not seek to follow Norway into the EEA precisely because she sought a UK solution that reduced the UK's financial commitments to the EU, increased the level of control over immigration and retained the best possible deal on trade in goods and services. Her statements on such matters, in particular those on retaining control over immigration and not being bound by the jurisdiction of the Court of Justice of the European Union, have resulted in the now often used phrase 'hard Brexit'.

The Swiss Model also appears unlikely to be adopted at this stage. Switzerland has a free trade agreement with the EU and a number of agreements which give it access to the single market for most industries. But it does not have full access to the single market for its banking sector and other parts of the services sector, which together make up close to 80% of the UK economy. Importantly, the Swiss Model also requires the free movement of people and payment into EU programmes, which, as discussed above, remain two of the most sensitive political issues post the Referendum. Both for these reasons and a recognition that bespoke arrangements such as those with Switzerland are not favoured amongst the EU, it appears unlikely that the UK would seek to follow Switzerland into EFTA in order to negotiate a bi-lateral agreement with the EU.

The Turkish model has arguably never been a genuine contender: it is not an economically favourable option, giving only partial access to the EU single market. Furthermore, whilst the customs union means Turkey faces no tariffs or quotas on industrial goods it exports to EU countries, the customs union does not apply to agricultural goods or services (both important issues for the UK) and Turkey also has no influence on the tariffs it may impose on goods it imports from non-EU countries – the customs union means that it must apply the EU's common external tariff (over which it has no control or influence) to those goods.

The Canadian Model is an example of an individually negotiated bilateral treaty with a third country *(i.e.* a jurisdiction that is not part of the EEA) in exchange for access to the single market. The Comprehensive Economic and Trade Agreement (CETA) took seven years to negotiate and although signed by Canada and all of the current 28 EU Member States it still requires ratification by the European Parliament. CETA gives Canada access to the single market for goods without all of the obligations that come with the Swiss and Norway models, such as contributing to the EU budget or signing up to free movement. The agreement removes trade tariffs in respect of industrial goods and many customs duties on agricultural products have also been substantially eliminated. However, perhaps crucially for the UK, CETA does not apply to services and, given the importance of the financial services sector in particular (to the UK more widely and specifically to London), it is difficult to consider that the UK would contemplate entering into such a complex bilateral arrangement unless it were tailored to the UK's own needs. Of course, it remains to be seen whether the EU has any appetite to agree a bespoke 'Canada Plus' style model with the UK given the implications for the 27 remaining Member States and the likely accusation that the UK will simply have cherry-picked all the best bits of EU membership with none of the obligations.

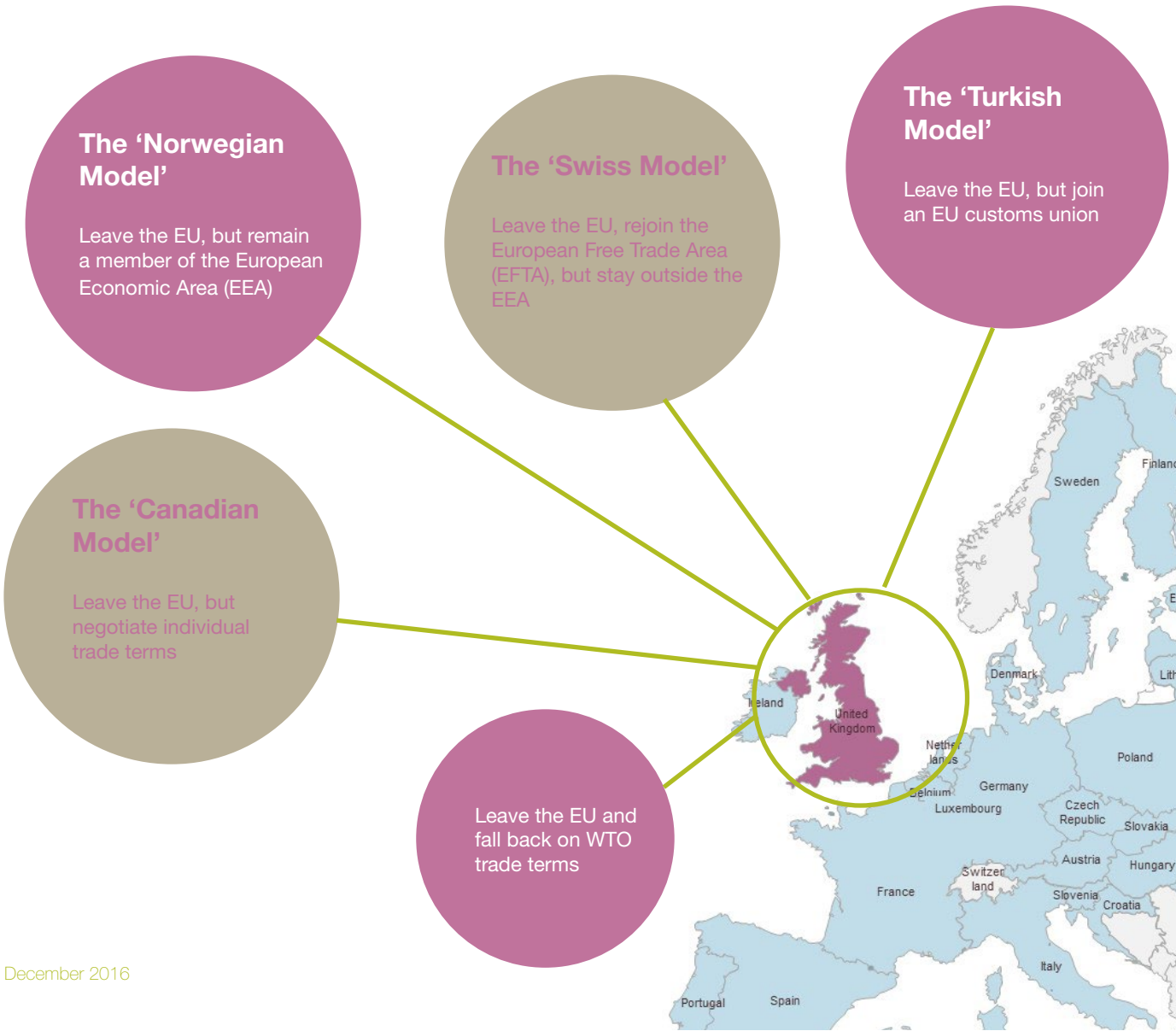
Finally, under the WTO model, the UK would adopt a unilateral free trade policy dropping all tariffs and relying on the WTO's framework like Hong Kong and Singapore. There are two primary WTO agreements: one that applies to the trade of goods and one to the trade of services. Under both agreements there are common fundamental principles: each WTO member must accord 'most favoured nation' treatment in respect of trade in goods and services supplied by each member of the WTO. Or put differently, each WTO member is generally prohibited from charging a lower tariff on goods originating in one WTO member than is applied to goods originating in another WTO member. The WTO rules will also be relevant to the UK's trade with other

countries in the world with which it does not enter into private trade agreements. One potential downside of the WTO model is that it could have an adverse effect on the UK's agriculture and manufacturing sectors as importing goods such as food and steel would largely be cheaper than producing them in the UK.

Furthermore, the UK is not presently a full member of the WTO – its relationship is partly individual and partly as a member of the EU. The EU has a single set of tariffs and commitments in respect of goods and services agreed with WTO members which apply to all EU Member States (including, presently, the UK). Once outside the EU, the UK will therefore need to negotiate its own schedules both with the EU (for example on how fairly to divide up existing 'tariff quotas') and with the rest of the WTO by consensus. Even then, under WTO rules, this would not include any preferential access to the EU single market, or to any of the 53 markets with which the EU has negotiated free trade agreements. It would also affect the price of imported goods paid by UK consumers, if reciprocal tariffs were imposed on imports from EU countries.

At this stage, some six months after the Referendum result, the only thing that we can say with some certainty is that there remains a vast amount of uncertainty concerning the final outcome. The UK appears to favour negotiating its own bespoke 'associate member' arrangement, perhaps using Canada as a model but going further in terms of access to the single market for services. But even this negotiating position has faced doubts not only from many of the remaining 27 Member States, but also by some key members of the UK's own Government, including the Secretary of State for International Trade and the Secretary of State for Exiting the European Union, both of whom have made recent pronouncements that do not suggest access to the single market (with all its costs as well as benefits) is a 'red-line' for the UK.

It is to be hoped that greater clarity will begin to emerge once negotiations start in earnest following formal notification by the UK of its intention to leave the EU under Article 50 of the Treaty on the European Union ('TFEU'). Yet even this step, which is stated to be "*in accordance with [a Member State's] own constitutional requirements*" is fraught with uncertainty and ongoing legal challenges as to whether this can be validly delivered by the Prime Minister under the Royal prerogative or whether it requires prior Parliamentary approval. The High Court (in which three Court of Appeal judges sat *en banc*) has recently ruled that the Government does not have the power under the Royal prerogative to give notice pursuant to Article 50 and that an Act of Parliament will be required before notice can be given. The Government has appealed this decision, with the appeal to be heard by the Supreme Court on 5 to 8 December 2016, and has indicated that it intends to give notice in March 2017. However, it remains to be seen whether it will be able to do so within that time frame if its appeal to the Supreme Court is unsuccessful.



How will Brexit affect different areas of law?

In the event of a 'hard Brexit', the most pertinent issues for UK biotech that we can foresee are financial ones. The EU funding of R&D is considerable. UK companies benefit significantly from the UK's reputation as a centre of scientific excellence. While the UK Government has committed to underwrite R&D funds currently provided through the EU's Horizon 2020 scheme if they are withdrawn in the event of a 'hard Brexit', the long term outlook for funding remains uncertain (we discuss some of the options later in this article). Patent Box' and other investment incentive schemes could be extended. The UK may also seek to establish bilateral agreements with third countries to allow access to collaborative funding (as Switzerland did in 1992). However, whether these initiatives can meet prior EU funding levels is unclear.

Patent law post-Brexit

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Patent law in Europe is for a large part derived from a non-EU instrument, the European Patent Convention ("EPC"), meaning that there is a reasonable degree of harmonisation across Europe. As such, many of the general principles of patent law in the UK will remain unchanged following Brexit as the UK will remain a signatory to the EPC. However, there are some areas where the law in the UK is derived from EU legislation, which will need to be considered and potentially amended on Brexit. Regulations (such as the SPC Regulation (Regulation 469/2009) will simply cease to have an effect on Brexit unless the UK implements some alternative legislation, whereas Directives that have been implemented in national law will still have effect, but it will no longer be mandatory for the UK to implement such provisions and therefore the national implementing legislation may be amended.

One EU-specific piece of patent legislation is the Biotech Directive (98/44/EC). This Directive principally governs what biotechnology inventions are patentable. Despite the fact that this is an EU legislative instrument, no change should be expected to the patentability of biotech inventions post-Brexit, as the provisions of the Biotech Directive have been expressly implemented in articles 52-53 EPC and Rules 26-34 of the Regulations Implementing the EPC. As such, the UK must maintain them in national law in order to remain a contracting state of the EPC, which should be unaffected by Brexit, regardless of its form. Nevertheless, there is the possibility that the EPO and the CJEU (if asked) could interpret the relevant provisions differently, leading to a divergence between the UK and the remaining EU member states. One potential lack of harmonisation on the interpretation of the exclusion from patentability under the Biotech Directive has recently been identified by the European Commission, which we comment on elsewhere in this publication.

One area where change could be made is in relation to the so-called 'Bolar-type' exemption from patent infringement. This exemption provides that conducting certain necessary clinical studies and trials does not constitute patent infringement, and derives from certain EU Directives (Article 10(6) of Directive 2001/83/EC, substituted by Article 1(8) Directive 2004/27/EC and Article 13(6) Directive 2001/82/EC, substituted by Article 1(6) Directive 2004/28/EC). It has been implemented in the UK by SI 2005/2759 and can be found in Section 60(5)(i) Patents Act 1977. Interestingly, the approach that national legislatures and courts have taken to implementation of the Bolar-type exemption differs across the EU, and until recently, it was accepted that the UK's exemptions for clinical trials were narrower than those in some other countries in Europe, in that only clinical trials conducted for the purpose of obtaining generic or other abridged marketing authorisations were exempted. However, following a consultation by the UK Intellectual Property Office which resulted in legislative change in 2014, the Government decided to extend the experimental use exemption, implementing new sections 60(6D)-(6E) Patents Act 1977, thereby expanding protection for drug testing beyond merely generic products and to include originator products. This broadly brings the UK into line with most of the rest of Europe. Given that a consultation has already taken place on this point relatively recently, and the legislative exemptions were extended at least in part on the basis of encouraging clinical trials to be conducted in the UK, it is unlikely that the UK Government will seek to further amend the Bolar-type exemption or experimental use provisions post Brexit, particularly in a way that would result in a narrower exemption to patent infringement than is currently provided for by EU legislation.

Will Brexit impact on funding of scientific research under the European Commission Framework Programmes?

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EU funding of research and development in the UK is considerable, with UK universities relying on the EU for around 16% of their total research income[1]. Much of this funding is carried out through the European Commission's 'Framework Programmes for Research and Technological Development', the current iteration of which is called "Horizon 2020".

Horizon 2020 not only funds research institutions but also helps high-potential SMEs to develop innovative ideas for products, services or processes that are ready to face global market competition.

While the result of the UK referendum will have no immediate effect upon the availability of funding under Horizon 2020, the possibility of Brexit raises fundamental questions as to how scientific research in the UK will be funded in the future and whether the UK will have access to funding provided through future framework programmes.

(i) What will happen to funding granted under Horizon 2020 before the UK leaves the EU?

The Treasury has confirmed that where UK organisations are granted funding from the European Commission while the UK remains a member of the EU (for example universities and businesses participating in Horizon 2020) those payments will be guaranteed by the Treasury, even when those projects continue beyond the UK's departure from the EU.

(ii) Can the UK retain access to the framework programmes if it leaves the European Union?

Certain non-EU countries such as Norway and Israel already participate in EU backed funding programmes, including Horizon 2020, as "associated countries". The UK could attempt to negotiate "associated country" status, as has been proposed by Universities UK, the representative organisation for UK Universities.

What associated country status might look like is far from clear; the 15 existing non-EU member nations that participate in Horizon 2020 do so on varying terms. The negotiation process could prove controversial for the UK as freedom of movement, a controversial issue during campaigning for the referendum, was viewed as a pre-requisite to Switzerland negotiating associated country status in 2014. What is clear is that without such an agreement it seems highly unlikely that the UK would have access to future framework programmes.

What will Brexit mean for funding for the UK Biotechnology sector from the European Investment Fund (EIF) and European Investment Bank (EIB)?

The EIF is majority-owned by the EIB, an institution which is in turn controlled by the governments of the 28 countries currently part of the European Union. The EIF was created in 1994 to foster innovation and the growth of small and medium-sized businesses in the EU. The EIF invests money in venture capital funds that then invest directly in businesses, to promote the creation and development of SMEs.

According to data from Invest Europe, between 2011 and 2015 the EIF committed €2.3 billion to 144 UK-based venture firms[2], amounting to nearly 37% of all venture funding raised in the UK during those years[3]. In particular, the life sciences sector has been one of the principal beneficiaries of EIF funding with funds such as the CRT Pioneer Fund, the IP Venture Fund and Imperial Innovations Group all receiving EIF investment.

For the time being, the EIF has stated that "it will continue to act within its current statutory remit and will not change its approach to operations in the UK". While this will provide some reassurance, the EIF's current rules provide that its investment is limited to EU member states, candidates to join the EU and members of the European Free Trade Association. Whether the EIF will be able to invest via the UK once the UK has departed from the EU therefore remains unclear, and will depend on the terms of departure negotiated by the UK Government.

"EU funding of research and development in the UK is considerable, with UK universities relying on the EU for around 16% of their total research income"

Tax issues arising from Brexit

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In the short term, the result of the referendum is unlikely to have a material impact on UK tax rules. It had already been announced, prior to the referendum, that the corporation tax rate was to be reduced to 17% by 2020 and the Chancellor has subsequently confirmed this in the Autumn Statement. Beyond that there are a number of ways that the UK tax regime could change as a result of no longer being bound by the EU Treaty.

Thinking about issues affecting the life sciences sector, the biggest hurdle for a number of tax reliefs is the rules on State Aid (i.e. where the provision of a tax relief is regarded as being an anti-competitive advantage to certain taxpayers over others). One of the many tax reliefs that requires notification for possible State Aid is research and development tax credit. Without the constraints of State Aid, the Government would, in theory, be able to provide much more generous tax reliefs and incentives to particular taxpayers or industry sectors.

VAT can also be a cost, or at least a material cash-flow issue, for many businesses in transactions. The rules on VAT are set out in an EU Directive, but once the UK is outside of the EU VAT Directive, it would, in principle, be free to create new zero-rated supplies (i.e. those supplies which allow the supplier to recover the VAT incurred in making the supply, but without having to charge any VAT to their customers). It could even abolish VAT altogether if it wanted to, although, given the revenue raising power that VAT has, this is pretty unlikely.

In the longer term, the UK may seek to promote itself as a jurisdiction with low taxes (but not an 'offshore' jurisdiction) in order to attract new investment. We might see further cuts in the rate of corporation tax (suggestions of a rate of 15% have already been floated, but it is not clear how serious they were) or more generous tax reliefs for R&D.

However, it will not all be plain sailing. Many of the changes that have been made to UK tax rules in the recent past have been as a result of the work of the OECD countries, and the UK's membership of that organisation is not affected by Brexit. UK tax issues that were a concern for the EU were also a concern for the OECD (the patent box being a good example). The fact that the UK is free of the rules of one organisation does not mean that it can abandon the commitments it has made to other international organisations. This may have a significant restraining effect on the extent to which tax policy can evolve. Also, as is the answer to so many Brexit-related questions: we shall have to wait to see what 'Brexit' actually looks like to gain a better idea of what the future might hold for UK tax for the life sciences sector.

Competition law

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Which of the Brexit options prevails in the long-term will determine to what extent (if at all), the EU competition rules continue to apply in the UK. Broadly speaking, the Norwegian model would result in no change to the status quo as regards competition law, whereas a 'hard Brexit' would result in greater autonomy for the UK regime which would, in effect, become a third country.

In the event of a 'hard Brexit', the UK would no longer be bound by EU rules on state aid would not be prevented from subsidising 'national champions', or, indeed, from extending the tax breaks available to research-driven organisations in a way which could have raised risks under EU law. The Government could decide to support the life sciences sector directly (as in the U.S.) by for example reallocating funds previously destined for the EU. Research areas unpopular with the EU Commission such as Genetically Modified Organisms could become focus areas. These issues were debated before the Referendum in a report published by the Science and Technology House of Commons Select Committee[4] which detailed the need for contingency plans to protect the life sciences sector in the event of a majority leave vote.

Increased transaction costs in mergers and acquisition may also be expected. Mergers and acquisitions have been a prevalent feature in the biotech industry and the fast approaching "Patent Cliff" has incentivised big pharma to acquire biotech companies to maintain patent pipelines. We cannot see that Brexit will necessarily slow this trend and indeed the deflated pound may make UK biotech companies attractive targets.

However, we do foresee potentially significant changes to merger regulation across the EU. Currently acquisitions affecting the UK (and all EU and EEA Member States) which meet the EU jurisdictional thresholds benefit from the 'one-stop' shop of the EU Merger Regulation. This means that one notification in Brussels is all that is required, with no need to seek separate national clearances. Under a 'hard Brexit', it is difficult to see how the UK would remain part of this arrangement and hence consideration of a parallel UK filing will be required. Furthermore, as a large economy in the EU, the fact that UK turnover will no longer count towards EU turnover for the purposes of the jurisdictional criteria may mean that fewer transactions meet the criteria for notification in Brussels at all which could therefore result in an increase in multiple national filings across the EU.

The UK's merger regime does not presently mandate prior notification and for this reason is often described as a 'voluntary regime'. In practice, however, all transactions which meet the UK jurisdictional criteria and which raise any, or any potential, substantive issues are likely to be notified in the interests of legal certainty. Given the above, there is likely to be a considerable increase in parallel national filings, requiring consideration of national competition clearance conditions and a consequent degree of duplication and increased costs.

As is the case more generally, it is too early to say much in relation to the future direction of UK competition law in the event of a 'hard Brexit', and how this will affect the biotech sector in particular. But at least in the short term there will be no practical immediate changes. Article 50 TFEU provides for a two year period to negotiate the terms of any exit and this period can – in principle – be extended by consent. There are also good arguments for considering that just as the UK has the unilateral right of whether and when to trigger an Article 50 notification, so it also has the unilateral right to withdraw its notification, provided it does so before the expiry of two years, or conclusion and adoption of an agreement on its terms of exit, whichever comes first (albeit this remains another area of some uncertainty which may yet be tested in the courts).

In any event, the fundamental principles of EU competition law have been adopted and enacted in UK legislation and it is unlikely that we will see any substantive changes to these laws, as they apply in the UK, in the foreseeable future (with the possible exception of jurisprudence relating to the creation and protection of the EU single market) . That said, a 'hard Brexit' would require the UK to consider the applicability of the block exemptions. EU block exemptions, including for example the Technology Transfer and Research and Development Block Exemptions, are currently directly applicable in EU Member States without the need for national implementing legislation. Once it ceases to be a member of the EU, consideration will need to be given as to whether the UK will need to implement specific national legislation to replicate the exemptions.

Of course, the UK might see this as an opportunity to attract investment and R&D and so choose to implement more permissive replacement block exemptions to seek to make the UK a more attractive venue for R&D and licensing collaboration compared to its European neighbours. More generally, if the UK is no longer part of the single market, this could result in the removal of certain limitations in the application of the block exemptions (i.e. those dealing with territorial restrictions aimed at protecting parallel trade and the single market).

In the longer term, the fact that an English court may decide that it is no longer under any obligation whether under Article 4(3) of the TFEU or under its duty of sincere co-operation to ensure consistency between UK and EU competition law, might result in greater divergence. But even then any changes will be incremental and we do not consider it likely that we will see a paradigm shift any time soon.

1 https://fullfact.org/education/how-much-money-do-british-universities-get-eu/
2 http://www.eif.org/news_centre/publications/country-fact-sheets/EIF_Fact-sheet_UK.pdf
3 http://www.investeurope.eu/research/activity-data/annual-activity-statistics/
4 Which can be found at http://www.publications.parliament.uk/pa/cm201617/cmselect/cmsctech/158/15802.htm

The impact Brexit has had on EU Trade Mark and Design Protection

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Has the UK's decision to leave the EU affected trade mark and design protection?
At the present time EU trade mark and design protection remains unchanged. This is likely to remain the case until Brexit actually happens, which it is anticipated will be at least two years from when article 50 is invoked and the formal negotiations for the UK's withdrawal from the EU begin.

What will happen when Brexit takes effect?
When Brexit takes place, the existing UK arrangements with the EU and the UK's trading arrangements with the rest of the world which rely on EU membership will lapse, unless replacements are agreed. This will affect unitary IP rights which currently have application across the 28 member states of the EU - including the UK.

What will happen to EU trade marks?
Once the UK leaves the EU, unitary IP rights such as the EU Trade Mark will cease to have effect in the UK. It is anticipated, however, that arrangements will be put in place to ensure either that EU trade mark rights are formally recognised in the UK as continuing to have effect, or by giving rights holders the opportunity to 'convert' part of the EU right into a national UK right.

What will happen to registered Community designs?
Registered community designs will also cease to apply in the UK when Brexit takes effect. Again, it is anticipated that arrangements will be put in place to recognise their continued effect or to give rights holder the opportunity to 'convert' part of the unitary right into a national right.

What about Community unregistered design rights?
Community unregistered design right is more problematic. As there is no formal 'registration' to convert to a national right, this protection may be lost unless the UK passes new legislation creating an equivalent right. The UK already has an unregistered design right which protects shape or configuration of a product (as opposed to the appearance of a product including surface decoration protected by the Community unregistered design right) and it is conceivable that this could be extended to bridge the gap in protection.

Should any action be taken now in relation to existing trade mark registrations?
Trade marks which are not put to genuine use within the EU for a period of 5 years become vulnerable to revocation. It is not clear how this use requirement will apply post-Brexit to an EU trade mark which has only ever been used in the UK (or indeed an EU trade mark which is 'converted' to a UK national right but which has only ever been used outside the UK). A fair outcome for brand owners would be to treat any use of a mark in the EU, during the period when the UK was still a member of the EU, as counting towards the genuine use requirement. Until more is known about how this will be dealt with, the safest position brand owners who wish to retain protection across these territories can put themselves in is to ensure usage both in the UK and elsewhere in the EU.

What about new trade mark applications?
An EUTM will continue to provide valid and enforceable protection in the UK until such time as Brexit takes effect. It is then likely that transitional provisions will operate to ensure continued protection in the UK for holders of EUTMs. If this were not to happen it would adversely affect and discourage brand owners' trade in the UK, something the Government would likely seek to avoid. For the time being, therefore, there should be no need to apply for separate UK and EU trade marks.

What will happen to seniority claims in EU trade marks?
Any UK seniority claims in an EUTM will cease to have effect from the date the UK exits the EU. Seniority claims from other EU member countries will not be affected.
We would advise retaining any UK national right which forms the basis of a seniority claim in an EUTM to ensure the best protection for the trade mark in the UK. Legislation may be implemented which allows UK national rights previously lapsed as part of a seniority claim to be restored.

What about international trade mark registrations?
At present, the validity of an existing International Registration based on an EUTM will be unaffected.

Once the UK leaves the EU, any UK based company looking to file a new International Registration will need to demonstrate that they have a real and effective commercial establishment in one of the remaining 27 EU member states. This is a requirement in order to meet the necessary criteria for filing an International Registration based on an EUTM, failing which it will be necessary to base an International Registration on a UK application/ registration.

An existing International Registration designating the EU may require conversion in order to obtain protection in the UK, meaning that a national right in the UK will be obtained without loss of priority or filing date.

"Once the UK leaves the EU, unitary IP rights such as the EU Trade Mark will cease to have effect in the UK."

Green light for the UPC

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Contrary to most expectations, and despite the result of the Brexit referendum, the UK will be ratifying the UPC Agreement. Announcing the news, UK Minister of State for Energy and Intellectual Property, Baroness Neville-Rolfe, said:

"The new system will provide an option for businesses that need to protect their inventions across Europe. The UK has been working with partners in Europe to develop this option… As the Prime Minister has said, for as long as we are members of the EU, the UK will continue to play a full and active role. We will seek the best deal possible as we negotiate a new agreement with the European Union. We want that deal to reflect the kind of mature, cooperative relationship that close friends and allies enjoy. We want to involve free trade, in goods and services. We want it to give British companies the maximum freedom to trade with and operate in the Single Market – and let European businesses do the same in the UK."

Does this really mean the UPC will go ahead, and if so when? Could it yet be derailed, and will the UK remain in the system when it leaves the EU? What will happen to the London branch of the Central Division (so important to the Biotech and wider Pharma sector) if the UK does not remain in the UPC? These are just some of the questions arising in the immediate aftermath of the announcement.

To answer these questions, we need first to consider what has already been achieved, and what remains to be done. From a practical perspective, the system is almost ready. In the nearly four years since the UPC Agreement was signed, the Preparatory Committee has driven the project forward to great effect. For example, the Court Rules are all but finalised, including setting the levels of Court fees. Likewise, the EPO has agreed the unitary patent rules and renewal fees, and agreed how those fees will be distributed to participating states. The main tasks remaining therefore are to complete the process of appointment of the judges and iron out the last remaining bugs in the IT system. This will need several more months' work, but should be achievable within the timescales we can now foresee from a political perspective. These timescales are that both the UK and Germany – the last two countries needing to ratify – will complete ratification by late spring 2017, and will be sufficiently near completion to allow the "Provisional Phase" of the UPC to begin by about April. Then within about six months, the UPC will open its doors for business and the EPO will be able to grant its first unitary patents.

The long term participation of the UK is less certain. The last thing anyone wants is to find that having joined the system, the UK then leaves again, meaning a yet further set of transitional arrangements being required to deal with things such as how pending actions are to be completed as regards the UK, and what happens to unitary patents in terms of their UK coverage. Uncertainty can only be bad for the system as users exercise more caution than they otherwise would have done. Unfortunately, there is little prospect of immediate clarity from the political perspective as the fate of the UPC becomes just another aspect of the Brexit negotiations. Happily there seems a real willingness among the participating states to find a way to allow the UK to continue as part of the venture. What is lacking, however, is any consensus as to how (from the perspective of legality of such an arrangement) this is to be achieved. Opinions range from the need for only minor adjustments, to it being impossible. Neither is there any mechanism in the UPC for a country to leave the system. Both of these issues need to be addressed quite urgently in the coming months. This is not being negative about the system, but is so that users of the system can have confidence in its future and to have answers to the inevitable questions.

What then of the future of the London branch of the Central Division of the UPC should the UK decide it must leave the UPC? On this, there seems actually to be no legal reason why any part of the Court could not be outside the EU. As Margot Fröhlinger (EPO, formerly of the Commission) has put it: there's no reason it could not be in Honolulu. Whether that is politically acceptable is another matter, but at least there would be no urgent need to find a new home for the Division should the UK leave the system on Brexit.

Finally for the politicians, there is one other issue which should not be overlooked. The future of SPCs derived from unitary patents remains uncertain. The present scheme would seem to be that unitary patents could be used in the same way as conventional European patents, as basic patents, and hence give rise to essentially national SPCs as at present. That seems very unsatisfactory for a unitary system. Hence, another matter which needs to be looked at again now that the UPC has been rescued from an early grave is the work on how to create a unitary SPC.

Hence there is a long political "to do" list, the main points being: find a way to keep the UK in the UPC and unitary patent system over the long term, cover off the possibility of the UK having to leave, and sort out unitary SPCs. For users also there is a "to do" list: decide upon future use of the unitary patent system, decide on opt-out strategies for existing and future "classical" European patents and their SPCs, and consider in conjunction with licensors and licensees how licensed-in and licensed-out patents should be treated (opted out or not). Suddenly time is short.

"Does this really mean the UPC will go ahead, and if so when? Could it yet be derailed, and will the UK remain in the system when it leaves the EU?"

Patent litigation

Our Patent Litigation practice

The majority of Bristows' IP lawyers have scientific and 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.

Arrow declarations – a second shot at the bullseye

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2016 is the year that the Arrow declaration has made its comeback.

These declarations concern pending patent applications and are so named after a case from 2007, *Arrow v Merck* [2007] EWHC 1900 (Pat). In essence, a party seeking to clear the way of a granted patent (which it is encouraged to do in the UK if it relates to a generic pharmaceutical product) can apply to revoke the patent prior to launch of a product. On the other hand, a party cannot do so in relation to pending patent applications as the law does not allow for pre-grant opposition. Nevertheless, the English Patents Court in the *Arrow* case held (in summary proceedings) that it was at least arguable that the Court had jurisdiction to grant a declaration that a particular product would have been anticipated and/or obvious at a given date in order to protect a manufacturer of that product from a subsequent claim for infringement of a later-granted patent having that date as priority date. This would support a defence that such product could not infringe a valid patent with that priority date, regardless of the form of the claims of that patent (a version of the so-called *Gillette* defence). Although the earlier *Arrow* case settled before trial, the Claimant in the recent case of *Fujifilm Kyowa Biologics v AbbVie* [2016] EWHC 2204 (Pat) has sought to rely on this jurisdiction for the second time in a year.

The background to the case – FKB 1

Fujifilm Kyowa Biologics (FKB) has been developing a biosimilar adalimumab product to AbbVie's blockbuster Humira® product. It had issued a claim in late 2015 to revoke two granted patents in AbbVie's name relating to dosage regimes for use of adalimumab in various clinical indications. In light of a number of pending divisional applications to those granted patents, FKB also sought a declaration (following the Arrow case) that a specific dosage regime for adalimumab would have been obvious at each of the claimed priority dates of the two patents in suit. Shortly after issue of the claim form, AbbVie indicated in opposition proceedings at the EPO that it no longer approved the text of one of the granted patents, leading the EPO to revoke that patent. Nevertheless, FKB wished to pursue its claim for an Arrow declaration in relation to the priority date of this patent due to the pending divisional applications, on which AbbVie sought summary judgment and/or to strike out. In his judgment from March of this year (FKB v AbbVie [2016] EWHC 425 (Pat)), Carr J held that the Court had jurisdiction to grant a declaration of the type sought and that FKB had a real prospect of succeeding at trial in persuading the Court to grant such a declaration on the sufficiently unusual facts of the case, even though he accepted that the jurisdiction needed to be exercised with caution.

The latest case – FKB 2

This second and recent case concerned another family of patent applications in AbbVie's Humira patent portfolio. These also relate to dosing regimens for adalimumab. In a new action, FKB again sought an Arrow declaration that a specific dosage regime for adalimumab would have been anticipated and/or obvious at the claimed priority date of this additional patent family. FKB also sought an injunction against AbbVie to restrain it from threatening or commencing proceedings for patent infringement in relation to acts covered by the declaration sought. AbbVie applied to set the claim aside in summary judgment and/or strike out proceedings.

In this second case, AbbVie accepted (subject to appeal) that the FKB 1 case had been decided correctly and that the jurisdiction to grant Arrow declarations existed. Nevertheless, AbbVie argued that, it being a jurisdiction that should be exercised cautiously, it should not be exercised on the facts of this second case which were different to those in FKB 1. On its part, FKB sought to rely on two principal facts to argue that AbbVie was seeking to shield its patent portfolio from the scrutiny of the English Courts and the EPO Opposition Division. First, it cited the fact that shortly before grant of a patent within the new family (i.e. after the EPO had

announced its intention to grant the patent), AbbVie had indicated on the last possible date that it no longer approved the text proposed for grant and sought to make narrowing amendments to the claims whilst expressly reserving the right to pursue the deleted subject matter by way of further divisional application(s). Second, FKB sought to rely on AbbVie's conduct in the FKB 1 case by way of similar fact evidence. In this case, Arnold J was persuaded that FKB had a real prospect of success against the patentee and allowed the claim to continue to trial.

FKB also sought the *Arrow* declaration against the AbbVie's UK affiliate (and MA holder for Humira in the UK), who is not the patentee. AbbVie resisted on the basis that the UK affiliate had not committed the acts in the EPO which were complained of and also that the UK company had no interest in the patent rights complained of. Arnold J was of the view that it could not be said that FKB had no legitimate interest in obtaining a declaration that was binding on the UK affiliate given that the latter party was the one with the most direct financial interest in FKB's proposed acts relating to its biosimilar adalimumab product, and therefore allowed the claim to proceed to trial.

Arnold J also reviewed the case law on anti-suit injunctions and concluded that the Court had the power to grant a domestic anti-suit injunction against a defendant over which it has jurisdiction where the defendant's threatened proceedings were vexatious, oppressive or an abuse of process. Nevertheless, this was a power that should be exercised with considerable caution. On the facts, the judge held that FKB had a real prospect of obtaining such an injunction (although not if it failed to obtain the declaration sought) and allowed the matter to proceed to trial.

As a final point, Arnold J also held that FKB's claim for an Arrow declaration fell within the exclusive jurisdiction of the UK courts pursuant to Article 24(4) of the Recast Brussels I Regulation, even though the declaration is formulated to cover a particular product rather than an as yet to be granted patent. This had the consequence that no permission was required to serve on the patentee (a Bermuda company) outside the jurisdiction, although Arnold J added that had he been wrong he would in any event have granted permission to FKB to serve out.

What happens next?

The Patents Court will now decide in both the FKB 1 and FKB 2 cases whether to grant Arrow declarations in each case. To date, the UK Courts have never granted an Arrow declaration, although the Hague District Court in the Netherlands did grant such a declaration in the Dutch Arrow case (relating to alendronate). The trial of the action in FKB 1 has been fixed to be heard in January 2017, whilst the trial of the FKB 2 action has been provisionally listed for a window of May to July 2017. In the meantime, the Court of Appeal has heard AbbVie's appeal in FKB 1 regarding the decision to allow FKB's application for an Arrow declaration to proceed to trial. The appeal hearing was held at the end of November 2016, and when the judgment is delivered it could potentially determine both that part of the first action that relates to the Arrow declaration and the second action.

CJEU: no punitive damages or restitution of infringer profits for Community plant variety right infringement

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In a recent decision (Hansson v Jungpflanzen Grünewald GmbH, C-481/14, 9 June 2016), the CJEU held that neither the Community Plant Variety Rights Regulation (2100/94) nor the Intellectual Property Enforcement Directive (2004/48/EC) provides for the payment of a flat-rate 'infringer supplement' or restitution of the infringer's gains and profits following infringement of a Community Plant Variety Right.

The case concerned an action for infringement of a Community plant variety right ('CPVR') in the Landgericht Düsseldorf (Düsseldorf Regional Court). Hansson, the holder of the CPVR, had been unsuccessful in an application for interim measures but in main action proceedings Jungpflanzen was found to have infringed the CPVR and Hansson obtained an order requiring Jungpflanzen to pay compensation for the damage resulting from its sales of infringing plants. Hansson was awarded damages based on the licence fee Jungpflanzen should have paid for the plants it had sold but the first instance Court refused his other claims for: (i) payment of an 'infringer supplement' to the licence fee; (ii) reimbursement of the costs related to the proceedings; and (iii) default interest on (i) and (ii). The 'infringer supplement' was considered by the Court to constitute punitive damages that are not provided for by the Community Plant Variety Rights Regulation (2100/94) (the '**CPVR Regulation**'), the Intellectual Property Enforcement Directive (2004/48/EC) (the '**Enforcement Directive**') or by national law.

Both parties appealed to the Oberlandesgericht Düsseldorf (Düsseldorf Higher Regional Court), which held that 'reasonable compensation', as provided for in the CPVR Regulation, should be set in the light of market licence rates during the period of infringement but noted that there appeared to be no basis in the CPVR Regulation for an automatic flat-rate increase in the compensation set, an order for indemnification of Hansson for his litigation costs (e.g. travel, meetings and time invested) or the costs of the unsuccessful proceedings for interim measures.

The Oberlandesgericht Düsseldorf stayed the proceedings and referred eight questions relating to Article 94(1) and (2) of the CPVR Regulation[5] and Article 13(1) of the Enforcement Directive[6] to the Court of Justice of the European Union ("CJEU").

Decision

Rather than responding to each of the Oberlandesgericht's detailed questions, the CJEU re-grouped the questions and provided responses to three queries that it considered the German Court to be asking 'in essence'.

5 Article 94 of the CPVR Regulation provides for the rightholder to claim 'reasonable compensation' for CPVR infringement (Article 94(1)) and, where the infringer has acted intentionally or negligently, to claim compensation for any further damage resulting from the act in question (Article 94(2)).
6 Article 13 of the Enforcement Directive provides that, when calculating damages, the court shall take into account all appropriate aspects including lost profits of the injured party, unfair profits made by the infringer and moral prejudice caused to the rightholder. In addition, the court may in appropriate cases set the damages as a lump sum on the basis of elements such as the amount of royalties or fees which would have been due if the infringer had requested authorisation to use the intellectual property right in question.

1. Nature of the compensation provided for in Article 94 of the CPVR Regulation

The CJEU confirmed that Article 94 concerns exclusively compensation for damage suffered by the rightholder as a result of the infringement, which must reflect the actual and certain damage suffered. As a result, Article 94 cannot be interpreted as providing a legal basis for the payment of punitive damages established on a flat-rate 'infringer supplement' basis, as these would not necessarily reflect the damage suffered by the rightholder. The CJEU considered this to be consistent with the objectives of the Enforcement Directive: recital 17 of the Directive states that remedies must take due account of the specific characteristics of the case; recital 26 states that the aim of any compensation is not to introduce an obligation to provide for punitive damages; and Article 13(1) states that damages must be appropriate to the actual damage suffered by the rightholder.

Furthermore, the CJEU held that Article 94 does not permit the holder of a CPVR to claim restitution of the gains and profits made by an infringer, since both 'reasonable compensation' under Article 94(1) and the amount of compensation payable under Article 94(2) must be set on the basis of the damage suffered by the injured party and not the profit made by the infringer. Although Article 94(2) refers to the 'advantage derived…by the person who committed the infringement' it does not provide that that advantage must be taken into account in the amount of the financial compensation actually awarded to the holder. As regards restitution, the national law of Member States should be applied pursuant to Article 97 of the CPVR Regulation. The decision of the CJEU makes no reference to Recital 26 or Article 13(1)(a) of the Enforcement Directive (both of which provide that judicial authorities shall take account of 'any unfair profits made by the infringer' when setting damages for infringement of intellectual property rights).

2. Methods for setting the compensation provided for by Article 94(1) of the CPVR Regulation

The CJEU held that the basis of 'reasonable compensation' pursuant to Article 94(1) should be an amount equal to the licence fee payable for licensed production of the plant variety (Geistbeck, C-509/10) and it is for the referring court to determine whether it is appropriate to increase the amount of that fee in light of the circumstances, bearing in mind that each circumstance may be taken into account only once. In addition to the fee that would normally be payable, 'reasonable compensation' includes all damage that is closely connected to the failure to pay that fee, including default interest. However, costs incurred for monitoring compliance with the CPVR are excluded.

3. Compensation for damage provided for in Article 94(2) of the CPVR Regulation

In order to obtain full and objective compensation for any further damage suffered pursuant to Article 94(2), the rightholder must produce evidence which establishes that its damage goes beyond the matters covered by the 'reasonable compensation' under Article 94(1). If the specific matters put forward by the rightholder are not quantifiable, a lump-sum method may be used.

Further, the CJEU noted that it is not contrary to Article 94(2) if the costs incurred in an unsuccessful application for interim measures or out-of-court expenses incurred in connection with a successful infringement action are not reimbursed by the rightholder. The decision notes that out-of-court expenses related to bringing the infringement action may be compensated if the rightholder would have otherwise been deterred from bringing legal proceedings to enforce its rights but no guidance is provided as to when out-of-court expenses would be so high as to deter the rightholder from doing so.

Comments

Following the conservative approach to damages taken by the CJEU in this decision, it seems unlikely that the holder of an infringed CPVR will recover more than 'reasonable compensation' (the market licence fee plus default interest) unless it is able to provide concrete evidence of further damage. The imposition of a flat-rate 'infringer supplement' or restitution of infringer profits and gains will not be possible under Article 94 of the CPVR Regulation, and the costs of an unsuccessful preliminary injunction and out-of-court expenses will not be recoverable unless it can be demonstrated that the exclusion of such expenses would deter rightholders from enforcing their rights.

The decision is disappointing in many respects, in particular in its failure to fully engage with the questions referred. For example, the CJEU provides no guidance on the interpretation of Article 13 of the Enforcement Directive despite a number of the questions from the Oberlandesgericht Düsseldorf being directed to this provision expressly. The CJEU makes only a single, passing reference to Article 13 of the Enforcement Directive, using it to justify a restrictive interpretation of Article 94 of the CPVR Regulation on the basis that Article 13(1) specifies that damages must (in the language of the CJEU) be 'appropriate to the actual damage suffered by [the rightholder] as a result of the infringement' (in fact, the English version of the Directive refers to 'the actual prejudice suffered', which could arguably support a broader interpretation of Article 94). Furthermore, on the question of restitution, the CJEU merely refers the issue back to Member States on the basis of Article 97 of the CPVR Regulation, without addressing the reference to damages taking account of unfair profits made by the infringer in Article 13(1)(a) of the Enforcement Directive.

The CJEU's refusal to address the Oberlandesgericht Düsseldorf's questions on Article 13 of the Enforcement Directive represents a missed opportunity to promote consistent enforcement throughout Europe, particularly since guidance on Article 13 would have applied not only to CPVRs but to all intellectual property rights covered by the Enforcement Directive. What is clear from the decision, however, is that rightholders should not expect a generous approach to damages for CPVR infringement on the basis of the CPVR Regulation.

Biosimilars: a litigation outlook

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Biosimilars are becoming increasingly established in both Europe and the US and it is also clear that in addition to proteins and peptides, biosimilar monoclonal antibodies (mABs) will form a greater part of the future global biological market. Biosimilar development is more complex than for small molecule generics, which leads to higher costs and a likelihood of premium pricing in the market, which could increase the burden on health services.

Against the context of this commercial outlook, in this article we will consider the litigation outlook for biosimilars from the perspective of patent exclusivity. Commercial and patent litigation considerations are usually closely intertwined: where there's money, there's litigation. The market for originator biologic products is huge: 50 billion dollars globally just for the mAB segment alone. So as biosimilar competition grows, can we expect to see an increase in the volume of biosimilar patent litigation?

The short answer is yes. From a slow start, we are now beginning to see a gradual rise in the number of litigation cases filed, both in Europe and the US. This article will focus on the cases filed in the courts of the UK, which is one of the few jurisdictions outside the US where court decisions are freely available and third parties can access written arguments.

A slow start

Until recently, almost all UK patent litigation cases on biologics concerned disputes between originator companies over competing original biologic products. There have been one or two cases concerning patented platform technology, such as Medimmune's phage display technique for antibody production[7] or, more recently, Regeneron's patent for transgenic mice[8], but by and large patent litigation has concerned battles between originators over patents blocking a specific product market, often a mAB product. Being the highest value biologic products, and also some of the most challenging to develop and bring to market, mABs can be viewed as the bellwether for biologics litigation, as reflected by the subject matter of the first biosimilar cases described below.

During 2012-2013 there was an initial bout of litigation activity in relation to biosimilar infliximab (originator product: Remicade®). Hospira challenged the validity of 3 patents owned by the Mathilda and Terence Kennedy Institute of Rheumatology Trust concerned with combinations of anti-TNF antibodies with methotrexate[9]. The case settled. Inflectra, Hospira's biosimilar infliximab product, was approved by the European Medicines Agency (EMA) a few months later, in September 2013.

The following year, things warmed up further when biosimilar trastuzumab (originator product: Herceptin®) took centre stage in the Patents Court with the beginning of what was to become 3 separate court actions to revoke 5 patents owned by Genentech[10]. Again, the challenger was Hospira, seeking to clear the way in respect of certain follow-on patents for dosage regimens and formulations in order to gain freedom to launch a competing biosimilar following the expiry of the basic patent protection for trastuzumab in July 2014. Some of the litigation remains ongoing at the appeal level but at least at first instance in the UK, Hospira was successful in revoking all patents challenged. However, biosimilar trastuzumab has yet to be authorised by the EMA.

In late 2015, litigation stepped up yet another level, with 2 separate actions filed against follow-on patents for rituximab (originator product: MabThera®) and a further 2 separate actions against follow-on patents for adalimumab (originator product: Humira®). Hospira was responsible for one of the rituximab actions[11], Celltrion the other[12]. The actions against the adalimumab patents were brought by Fujifilm Kyowa Kirin Biologics[13] and Samsung Bioepis together with Biogen[14]. Suddenly, it appears that biosimilar litigation has become popular.

Patent thickets

Thus far, biosimilars have not been challenging the basic patents protecting the mAB molecules themselves. This is not surprising - these are typically very robust patents, respected by competitors. It was notable, for example, that in the trastuzumab litigation, Hospira mounted its first challenge significantly before the basic patent expiry but did not challenge the basic patent itself. In relation to infliximab, it was publicly reported that Hospira and other licensees of biosimilar products were waiting out basic patent expiry before entering the market[15].

However, surrounding the basic patent protection of any drug product is a penumbra of other patents. Sometimes called follow-

"The market for originator biologic products is huge: 50 billion dollars globally just for the mAB segment alone."

7 Medimmune v Novartis [2011] EWHC 1669 (Pat)
8 Regeneron v Kymab [2016] EWHC 87 (Pat)
9 High Court case number HC12B 01969: Hospira -v- The Mathilda and Terence Kennedy Institute of Rheumatology Trust
10 Hospira v Genentech [2014] EWHC 1094 (Pat) (10 April 2014); Hospira v Genentech [2014] EWHC 3857 (Pat) (21 Nov 2014); Hospira v Genentech [2015] EWHC 1796 (Pat) (24 June 2015)
11 High Court case number HP-2016-000002: Hospira v Biogen
12 High Court case number HP-2015-000059: Celltrion v Biogen
13 High Court case number HP-2015-000053: Fujifilm Kyowa Kirin Biologics v Abbvie
14 High Court case number HP-2016-000016: Samsung Bioepis v Abbvie
15 "Infliximab biosimilars to launch in the UK as innovator product reaches patent expiry" The Pharmaceutical Journal 19 February 2015.

on, or secondary, patents, these typically protect a number of associated inventions connected to the drug, such as the method of administration, therapeutic use, dosage regimen or formulation. For some of the top-selling biologic molecules, there are a vast number of follow on patents, the term of which far outlasts the basic patent but the strength of which can vary. These are the targets of biosimilars seeking to gain access to the market.

By way of example, it was argued in the ongoing UK adalimumab litigation that there were no fewer than seventeen follow-on patent families, each family deriving from the same application, and within each such family often at least one divisional application and sometimes more[16]. It was argued that this created "a dense thicket of patents" around Humira, albeit that this was a point on which the judge did not consider it necessary to make a finding of fact.

EPO oppositions

One way through such a thicket is to challenge the patents centrally upon grant at the European Patent Office (EPO), where applicable. European patents granted by the EPO take the form of a bundle of national rights, which must be invalidated country-by-country under national court or patent office proceedings. However, for a brief 9 month period, it is possible to oppose the grant of the patent centrally via opposition proceedings. If successful, this clears the entire bundle in one fell swoop. Unfortunately, once commenced, the duration of opposition proceedings at the EPO is extremely variable, sometimes taking many years and even as long as a decade once appeal proceedings and possible remittal back to first instance takes place. Nevertheless, the opportunity to knock-out patents centrally remains highly attractive to competitors, particularly given the relatively low cost of this procedure when compared to most national litigation systems.

Clearing the way

Invalidating patents in advance is not essential before launch of a biosimilar product but it usually seen as a prudent strategy, as illustrated by the examples of trastuzumab and adalimumab in the UK. Biosimilars are the products of significant technical development and considerable financial investment. To jeopardise this by launching "at risk" is not a decision to be taken lightly or without careful calculation. The risk of launching with patents still in force is that the product could be immediately injuncted on a preliminary basis (pending trial) - future sales stopped and potentially even existing sales recalled, damaging both commercial supply and reputation in the marketplace.

In order to avoid a preliminary injunction, the extent to which efforts must be made to invalidate patents in advance – for example, whether it is necessary merely to initiate invalidity proceedings or whether it is necessary to progress the proceedings to a conclusion – depends on jurisdiction. In some countries, such as Germany and Austria, national invalidity proceedings cannot be initiated at all during the pendency of EPO opposition proceedings. In the UK, the prevailing jurisprudence indicates that where there is a risk of infringement, competitors must make reasonable efforts to "clear the way" before launch if a preliminary injunction is to be avoided. Recent cases such as *Novartis v Hospira*[17] and *Napp v Dr Reddy's and Sandoz*[18] have indicated that the courts' expectation that a generic pharmaceutical company should clear the way before launch includes not just first instance invalidity proceedings but appeal proceedings too. This means planning ahead, ideally 2 or 3 years in advance. Given the difficulties in receiving regulatory approval for biosimilars, this means that decisions on litigation strategy may have to be taken before certainty is achieved in respect of the product launch date. One might think that it is prudent, therefore, to err on the side of caution. But clearing the way too early, long before product approval, carries the risk that a competitor takes the benefit of the clearance by being first to market, without having to carry the burden of the litigation, including its costs. It also carries the risk of a counterclaim for infringement and a *quia timet* injunction, as reported elsewhere in this publication in relation to the recent case of *Actavis v ICOS*[19].

Pending applications

Patent thickets include not just granted patents but pending applications. How is a biosimilar manufacturer to achieve certainty that it is free from the risk of patent infringement not just upon launch but throughout its life on the market? Can steps be taken to mitigate infringement risk in respect of future patents?

This is a topical question because it lies at the heart of both the adalimumab cases presently pending in the UK[20]. In these cases, Fujifilm and Samsung Bioepis are seeking a declaration from the court that their biosimilar adalimumab products are nothing more than known embodiments or obvious modifications of the state of the art at the date on which Abbvie's pending Humira patents were filed. The effect of such a declaration would be to neutralise the effect of Abbvie's pending patents because if the biosimilar products were already known, or were obvious at a certain date, then any future patent which covered such products and having the same priority date would be held invalid for lack of novelty or lack of inventive step.

It remains to be seen whether the court will grant the declarations sought but in a decision from March this year[21] it has already indicated that, in principle, such a declaration is possible, based upon an earlier precedent concerning the drug alendronate: *Arrow Generics v Merck*[22]. An appeal against this decision is currently pending, to be heard in late November 2016. The Arrow case settled before it reached trial so such a declaration has never yet been granted in the UK, albeit that the parallel Dutch case did progress to judgment in the District Court of the Hague, which granted the declaration sought, finding[23] that the generic alendronate tablets were an obvious modification of the state of the art.

The case law to date on these so-called "*Arrow* declarations" suggests that they will not be suitable in every case. For instance, the biosimilar product must be defined in strict terms – for example a specific dosage regimen for a particular indication as was the case in the alendronate and adalimumab cases. This may not work so well if the pending applications concern a formulation and if there is some doubt about whether the biosimilar would be formulated in the same way. Also, it is possible that the court will only consider making a declaration if the biosimilar manufacturer is also contesting the validity of granted patents at the same time or previously, and hence has a reason to be in court. It would put an onerous burden on the court system if cases could be brought in respect of pending patents alone. There is a further case on

16 Fujifilm Kyowa Kirin Biologics Co Ltd -v- Abbvie Biotechnology Limited [2016] EWHC 425 (Pat) at §12.
17 [2013] EWCA Civ 583
18 [2016] EWHC 1581 (Pat)
19 [2016] EWHC 1955 (Pat)
20 See cases referred to in footnotes 7 and 8
21 [2016] EWHC 425 (Pat)
22 [2007] EWHC 1900 (Pat)
23 Court of the Hague decision of Judges van Peursem, Brinkman and van Oostveen dated 13 February 2008

this issue, concerning additional pending adalimumab patent applications, which we report on elsewhere in this publication[24]. The court may ask the applicant in such cases to wait for the threat of such patents to materialise, or at least clarify, once the wording of the claims is finalised or the proprietor's intention to pursue prosecution is manifest. The decision of the courts in the adalimumab cases is awaited with interest.

Injunction prospects

Whether the courts would grant preliminary injunctions against biosimilars with the same readiness that they have done so in relation to small molecule generics is not yet certain. At least in the UK, the courts have been willing to grant injunctions on small molecule patents, in large part because competition between generics is so fierce that once the market is entered by one generic, there is a "feeding frenzy" of activity by others which serves to drive the price of the originator product down to a level from which it will never recover. The need to prevent this irreparable harm pending trial is usually a winning argument in preliminary injunction applications. However, it is not clear that the same considerations would apply to biosimilars. Unlike small molecule generics, which are able to obtain a marketing authorisation relatively cheaply and quickly, biosimilars are much more heavily invested and hence fewer in number. Therefore it is unlikely that there would be the same ferocity in competition and perhaps less price pressure as a result. A stable duopoly may be possible, in which case damages, rather than an injunction, may be an adequate remedy for an originator seeking to protect its position pending trial on the question of patent infringement.

Conclusion

From a slow start, biosimilars patent litigation is now well under way. At least in the UK, the litigation is following the traditional "clearing the way" model in which competitors are seeking to revoke originator patents prior to product launch. Such patents are usually follow-on patents covering aspects of the originator product such as its dosage regimen or formulation. These patents are often so prolific that, in a bid to seek lifetime freedom for their products, some biosimilars are pursuing novel clearance strategies designed to neutralise pending originator patent applications in addition to granted patents. Being heavily invested in their products is likely to make biosimilar manufacturers more risk averse in litigation, but it also means that there are fewer competitors on the landscape, relative to small molecule pharmaceuticals. Whether this means that the injunction risk is lower remains to be seen.

Transgenic mouse patents invalid for insufficiency

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Earlier this year, Carr J in the English Patents Court gave judgment in a biotechnology case that must rank as one of the most technically complex patent cases ever to have been heard in the UK (Regeneron v Kymab & Novo Nordisk[25]). Whilst the technical aspects of the judgment are far too lengthy and complex to discuss here, the judgment demonstrates the ability of the English court system and its judges to handle all manner of technically complex patent cases in an efficient and yet detailed manner.

Background

In this case, Regeneron's patents related to transgenic mice that can be used as platforms for therapeutic antibody discovery, in particular the replacement of mouse variable (VDJ/VJ) gene with human variable genes to produce immunoglobulin loci that will undergo the natural process of rearrangement during B cell development to produce hybrid antibodies. The first defendant Kymab was offering various strains of transgenic mice to the pharmaceutical industry. Regeneron alleged these infringed both patents in suit, and both Kymab and Novo challenged the validity of both asserted patents.

In addition to giving a lengthy explanation of the technology, the judgment includes interesting conclusions on construction of product-by-process claims and on applying the statutory test of insufficiency where it is alleged that an invention is not enabled across the breadth of the claim.

The Court construed all of the claims in dispute broadly. This analysis included the product-by-process claims, which were to a genetically modified eukaryotic cell, mouse embryonic cell, or mouse, in each case "obtainable by" methods described in a process claim on which the product-by-process claims were dependent. That process claim was to a particular type of genetic modification to a part of the immunoglobulin heavy chain variable gene locus such that human heavy chain variable region genes are introduced in the endogenous position of the mouse locus, so as ultimately to create a reverse chimeric antibody. This process allows the creation of transgenic mice producing humanised antibodies whilst leaving the mouse constant region intact, leading to greater viability and fertility of the mice. Once harvested, the mouse constant region of these antibodies can be replaced by a human constant region without loss of affinity or potency. These transgenic mice therefore provide an alternative and potentially better platform for therapeutic antibody discovery of fully human antibodies than using phage libraries or transgenic mice expressing fully human antibodies.

Insufficiency – process claim

In this case the breadth of all the claims in dispute, properly construed, led to problems on sufficiency. The judge noted that for a claimed class, the claim will be insufficient if the invention does not work with substantially all of the products or methods falling within the scope of the claim, following the Court of Appeal in the earlier case of *Regeneron v Genentech*. Whilst the judge recognised that the subject matter of the patents was highly complex and a significant amount of work would be expected to be required to develop it, the policy of encouraging innovation in highly technical fields needed to be balanced against the importance of guarding against patents which required invention on the part of the skilled person to implement and where the scope of claims exceeded the technical contribution.

On the facts, the judge held that the specific process claim that characterised the "obtainable by" claims was insufficient as it did not enable the insertion of genomic fragments of the size required in order to achieve the replacement of the gene segments described without undue burden and without invention. None of the methods disclosed in the patent would have worked. The judge did accept that the skilled person was entitled to apply their common general knowledge in the event of failure of the methods disclosed and if an obvious, standard approach would occur to

24 Fujifilm Kyowa Kirin Biologics v Abbvie [2016] EWHC 2204 (Pat)
25 [2016] EWHC 87 (Pat)
26 [2014] EWHC 3587

the skilled person then this would be an answer to the objection of insufficiency. In this case, however, none of the proposed alternative approaches were held to have been ones that would have occurred to the unimaginative skilled person.

Product-by-process claims

As to the product-by-process claims, the judge summarised the principles derivable from the judgment of Birss J (at first instance) in *Hospira v Genentech*[26] in relation to "obtainable by" claims as follows:

(i) their purpose is to claim a product irrespective of how it was made but with a shared characteristic which results from using a given process;

(ii) the claim has to specify the characteristic being referred to;

(iii) "obtainable by" claims present clarity problems and should only be permitted if there is no alternative way of defining the product in question; and

(iv) for a product to be "obtainable by" a process it must have every characteristic which is the inevitable consequence of that process.

The scope of the product-by-process claims therefore extended to products (cells and mice) which contained the introduced genes in the endogenous position regardless of the method used, even though the claimed process by which the products were "obtainable by" described only one such method. This conclusion was in line with the arguments of the patentee Regeneron. On sufficiency, the judge had held that these "obtainable by" claims were therefore of a considerably wider scope than the method claim, and thus insufficient, for the reasons given above in the section on sufficiency. He also held that even if he had concluded that the underlying process claim was not of excessive breadth, the wider product-by-process claims were still insufficient as they extended to cells and mice in which the entire mouse locus in question had been replaced by the entire human locus.

The other invalidity attacks of added subject matter, lack of novelty and lack of inventive step were all rejected, and the judge also ruled that, had the patent not been invalid, it would have been infringed by Kymab's mice strains. However, it is worth noting in passing that the patentee took an unusual approach in calling three witnesses of fact, in addition to the experts, to support its argument on inventive step. The first two witnesses, who were active in the field at the priority date although not employed by the patentee, gave evidence that the idea of modifying the particular locus (to create a reverse chimeric antibody) never occurred to them or their colleagues. The third witness was one of the inventors of the patent and explained how he arrived at the concept of a reverse chimeric locus. The written evidence of all three witnesses was not challenged at trial, and the judge held that their evidence provided a useful insight into the thought processes of leaders in the field at the priority date on inventive step. It is somewhat unusual to call the inventor as a witness in English patent litigation and it will be interesting to see if this marks the start of a new trend.

European Commission notice calls into question the decision in Tomato II and Broccoli II

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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. After a lengthy legal saga, the European Patent Office's (EPO) Enlarged Board of Appeal (EBA) clarified the matter in decision G2/12 and G2/13 (Tomato II and Broccoli II) allowing the patentability of such products even if they were inevitably derived from using '*essentially biological processes*'. The decision was based on a lengthy and in-depth analysis leading to the conclusion that a narrow interpretation of the exception to patentability was appropriate.

The law therefore seemed settled until in November 2016 the European Commission published its notice in response to the European Parliament Resolution of December 2015 asking the Commission to consider various issues concerning the Biotech Directive (Dir 98/44/EC). The Biotech Directive, like Article 53(b) EPC, includes an exclusion from patentability of '*essentially biological processes*' but does not expressly state whether products of such '*essentially biological processes*' are patentable. However, the recent Commission notice considers the negotiation of the Biotech Directive and its provisions in reaching the conclusion that the same result would not have been reached in the European Union context. Rather the European Union legislators' intention when adopting the Biotech Directive was, in the opinion of the Commission, also to exclude from patentability products obtained by means of essentially biological processes.

The application and interpretation of the Biotech Directive will fall to the courts of European Union member states and, in this regard, the Commission notice expressly states that it is intended only to assist in the application of the Directive and only decisions of the Court of Justice of the European Union (CJEU) will be binding. However, this leaves 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 seems a distinct possibility in such circumstances.

What impact will the notice have on the EPO?

In 1999 the EPC Implementing Rules were amended to insert the main provisions of the Biotech Directive and the EPO should therefore take the Directive into consideration when considering patentability. However, the EPO is not bound by the views of the European Commission or indeed by any future decisions of the CJEU. The EPO has now published a Notice (dated 24 November 2016) confirming that all examination and opposition cases "in which the invention is a plant or animal obtained by an essentially biological process" would be stayed ex officio. The Notice does not specify how long proceedings will remain stayed, but it does disclose that the EPO is discussing this issue with the European Patent Organisation member states and, "should the […] member states follow the interpretation offered by the European Commission Notice, the EPO will implement their decision".

Clear the way but careful where you tread

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A generic should clear the way

Following the seminal decisions of Jacob J (as he then was) in *Smithkline Beecham v Generics*[27] and *Smithkline Beecham v Apotex*[28], it has been accepted that a generic pharmaceutical company who plans to launch a generic product should seek to "clear the way" of any patent he might infringe by starting (and finishing) a revocation or declaratory action against that patent before launching onto the market. In *Novartis v Hospira*[29], the Court of Appeal confirmed that a generic should clear the way for his product not just in the High Court but in the Court of Appeal too[30].

In *Merck v Teva*[31], Teva did not seek to clear the way and Mr Justice Birss granted Merck a permanent injunction to prevent Teva from infringing its patent, notwithstanding that Teva at that stage had not committed an act of infringement. In his judgment Birss J stated that "*the questions the court is asking in every case [regarding a quia timet injunction] is whether, viewed in all the relevant circumstances, there was a sufficiently strong probability that an injunction would be required to prevent the harm to the claimant to justify bringing proceedings.*" A *quia timet* injunction is one granted in order to prevent threatened rather than actual infringement. The judge added that, in determining whether to grant such an injunction, the Court should look at the generic's objective and subjective intentions with regard to the potential infringement.

"...this leaves national courts enforcing granted patents having to resolve the conflict themselves"

Does clearing the way support an injunction?

On 10 August 2016, Birss J handed down his judgment in *Actavis v ICOS*[32]. In this case (which was in fact four cases joined together), Birss J was faced with many issues regarding the validity of two of ICOS' patents. The part of the judgment concerning infringement consists of only a small fraction of the decision (11 paragraphs of the total 491 paragraphs). However, in these paragraphs, Birss J addressed the question of whether "*a generic pharmaceutical company can seek to clear the way with a revocation action, with a contingent intention to launch a product if the action succeeds, without being held to be threatening to infringe the patent and thereby subject to an infringement counterclaim?*"

Birss J followed his approach in *Merck v Teva* with regard to *quia timet* injunctions and found the relevant objective factors to be: (i) the large and valuable market; (ii) the MAs granted to the generics; and (iii) the revocation proceedings brought by the generics. He stated the relevant subjective factor was that the generics' intention to launch was contingent on the revocation of the patents but noted that intentions can change and that no undertakings regarding the contingency of a launch had been given. Looking at the position overall, Birss J found that ICOS' infringement counterclaim was justified by the sufficiently strong possibility that a permanent injunction would be required to prevent the generics from infringing its patents until their expiry. In doing so he said that "*[b]ringing proceedings to revoke [the patents] is not proof of an intention to sell but it also supports the inference based primarily on the marketing authorisation" and that "the inference on which this quia timet infringement action is based does not derive solely or even predominantly from the fact [the generics] have sought to clear the way by applying to revoke patents. It derives from the marketing authorisation process.*" Therefore, it was the combination of having a granted MA and starting a revocation action to clear the way that gave rise to the injunction.

So should a generic clear the way or not?

A generic planning to launch a generic product needs to clear the way of any patents it would infringe to prevent the risk of it being subject to an injunction. Such a generic also needs to get a granted MA for his generic product because, in clearing the way, it may open the floodgates to other generics and will want to place itself in the best position it can to be the first generic product on the market following patent revocation. Starting the MA process once the path is clear would be leaving it too late.

As matters now stand, it appears that to avoid being subject to a *quia timet* injunction, a generic may not only have to clear the way but also provide an undertaking to the relevant patentee that it will not launch its generic product unless the patent is revoked or until the patent expires. This should give the patentee some comfort that an injunction does not need to be put in place, and thus remove the threat that serves as basis on which to grant a *quia timet* injunction.

27 Smithkline Beecham v Generics (2002) 25(1) IPD 25005
28 Smithkline Beecham v Apotex Europe [2002] EWHC 2556 (Pat)
29 Novartis v Hospira [2013] EWCA Civ 583
30 A similar approach was taken in Napp v Dr Reddy's [2016] EWHC 1581 (Pat)
31 Merck Sharp Dohme v Teva [2013] EWHC 1958 (Pat)
32 [2016] EWHC 1955 (Pat)

Plausibility in patent law: an unsettled concept

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What is plausibility in patent law?

The concept of plausibility in patent law is neither a requirement of the European Patent Convention (EPC) nor the Patents Act 1977, but has sprung out of the case law of the European Patent Office (EPO) and has been followed and developed further by the English court. Far from being a separate ground of invalidity, the plausibility of an invention is considered mainly in the context of obviousness and insufficiency, but has also been considered in the context of priority, novelty and industrial applicability.

For a patent to be valid, the technical contribution that is made to the art by the claimed invention must be plausible. 'Plausible' means that there must be some real reason for supposing that the statement is true[33]. It is a threshold test which is satisfied by a specification which discloses enough information to make the purported invention 'credible' as opposed to speculative[34]. The amount of information required to meet this threshold will depend on the patent in question but it is important to note that the rationale behind this test is to eliminate speculative patents where the claimed technical contribution is based on mere assumption.

Where did plausibility come from?

The traditional approach of the EPO to inventive step is central to understanding the concept of plausibility. This approach first requires the identification of a technical problem that is not solved by the prior art and second the identification of whether the claimed invention solves this technical problem. This is known as the problem/solution approach. For an invention to be plausible the specification must make it credible that the claimed invention solves the claimed technical problem.

The concept of plausibility has its origins in the decision of *AgrEvo*[35], which concerned a product claim for a class of chemical compounds for use as herbicides. The Technical Board of Appeal (TBA) of the EPO stated that in order to be patentable, a selection of compounds must be justified by a technical effect that is credibly achieved in substantially all of the compounds claimed and cannot be merely arbitrary. In this case, it was not credible that substantially all the compounds within the scope of the patent exhibited the claimed technical effect of herbicidal activity and so the patent was held invalid on the basis of obviousness since there was nothing inventive in making the compounds.

The word 'credible' was expressed as 'plausible' in a later case[36], where the TBA concluded that a patent application must contain sufficient detail to make it 'at least plausible' that a solution has been found to the technical problem which the patent in question purportedly solves.

The first time that plausibility was considered by the UK courts concerned a patent claiming the use of taxol-coated stents to prevent restenosis[37]. In the absence of any data in the patent showing that taxol would actually work to prevent restenosis, the High Court and Court of Appeal assessed the question of obviousness by reference to whether taxol might work rather than that it would work. In doing so they found the patent to be invalid for lack of inventive step over the common general knowledge (and that the patent was merely speculative). On appeal to the House of Lords, however, the patent was held valid. The House of Lords held that the specification did not need to contain data to support the invention if the specification made the invention plausible, which it did, and that on the facts of the case it was not obvious that taxol would work in preventing restenosis. A two-stage approach therefore arose: if the plausibility test is satisfied, the court will proceed to determine whether the patent is obvious according to established UK law.

Plausibility in the context of sufficiency

Whilst plausibility can be considered in the context of obviousness, priority, novelty and industrial applicability, arguably the most interesting developments regarding plausibility in relation to pharmaceutical patents have been in the context of sufficiency.

For a claim to be sufficient, the specification must disclose the invention in a manner which is clear enough and complete enough for it to be performed by a person skilled in the art[38], and to the full extent of the monopoly claimed[39].

The first of the leading cases in England and Wales on plausibility in the context of sufficiency is the *Regeneron* case[40]. In this case, the Court of Appeal held that a patentee does not have to demonstrate that an invention works across the full scope of the claim; instead, it must be plausible that the invention works across substantially the full scope of the claim:
"100. It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction

"...if the plausibility test is satisfied, the court will proceed to determine whether the patent is obvious according to established UK law."

then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case. 101. On the other hand, if it is not possible to make such a prediction or it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient."

The two-stage test was later summarised by Mr Justice Arnold[41] as follows:
"The first stage is to determine whether the disclosure of the Patent, read in the light of the common general knowledge of the skilled team, makes it plausible that the invention will work across the scope of the claim. If the disclosure does make it plausible, the second stage is to consider whether the later evidence establishes that in fact the invention cannot be performed across the scope of the claim without undue burden. In some cases, it is convenient to divide the second stage into two, first considering whether the invention can be performed without undue burden at all and then whether the claim is of excessive breadth."

The *Regeneron* decision has since been cited with approval by the Court of Appeal in two recent judgments: *Warner-Lambert v Mylan*[42] and *Idenix v Gilead*[43].

Therefore, whether a specification makes the claimed invention plausible is a threshold test that is satisfied where it allows the skilled person to "make a reasonable prediction that the invention will work with substantially everything falling within the claim"[44].

What level of disclosure satisfies the plausibility threshold?

In relation to medical use patents, the TBA held in *Salk*[45] that the claimed medical effect must be made plausible by the disclosure of the patent. To this end, the plausibility threshold may be satisfied by the disclosure of in vitro data, where such disclosure shows a clear and accepted relationship between the effects of the claimed compound and the target disease in question. The Court of Appeal in *Regeneron* agreed with the TBA and confirmed that a patentee *"must show, for example by appropriate experiments, that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible"*. It would be too great a burden on the patentee to have to show that the compound in question has approval as a medicine.

The patent in suit in *Regeneron* was attacked on the basis of insufficiency in two ways: that the claims extended to a very wide class of diseases, namely all non-neoplastic neovascular diseases (i.e., non-cancerous diseases involving cellular proliferation and angiogenesis) such that it was not possible to make a reasonable prediction that anti-VEGF therapy would be effective in the full range of diseases (insufficiency for excessive claim breadth); and that the patent claimed all known VEGF antagonists such that it would take undue effort to identify which antagonists worked for which diseases (classical insufficiency). Read in light of the common general knowledge, the patent was held to disclose a principle of general application that all neovascular diseases (neoplastic and non-neoplastic alike) were linked by the common thread of angiogenesis, that VEGF was necessary for pathological angiogenesis, and that it was reasonable to predict that a strategy for treating excessive angiogenesis in neoplastic diseases would also be effective to treat such angiogenesis in non-neoplastic diseases. Therefore, despite the fact that the data in the patent related to the inhibition of angiogenesis in neoplastic diseases only, the principle of general application disclosed made it plausible that the claimed VEGF inhibitors could be used to treat the wide range of non-neoplastic diseases referred to in the patent. As a result, the patent was held valid.

How is the plausibility threshold being applied by the English courts?

In one of the recent Hospira and Genentech cases, Hospira sought revocation of Genentech's patent relating to a particular dosing regimen of its trastuzumab drug used for the treatment of HER2-positive breast cancer[46]. The specification contained a relatively large amount of data, including pharmacokinetic data, pharmacodynamic data, mouse data and clinical trial results of a different dosing regimen (the 4 + 2 every 1 week regimen), but did not contain clinical trial results of the claimed dosing regimen (the 8 + 6 every 3 weeks regimen). In relation to the claimed regimen, the specification proposed a clinical trial but did not report any results and as such, the specification was considered *"entirely prophetic"*.

In light of *Salk* and *Regeneron*, such a large amount of disclosure might, on first impression, have been considered sufficiently detailed to make the claimed invention plausible. However, Mr Justice Birss decided that the key question in relation to the plausibility and sufficiency of the dosing patent was whether the skilled team would have the confidence to conduct a clinical trial of the 8 + 6 every 3 weeks regimen on the basis of the data disclosed in the patent read in light of their common general knowledge. Mr Justice Birss held that despite the data disclosed, the specification would not give the skilled team the confidence to carry out a clinical trial of the claimed dosing regimen and as a result the claimed invention was not plausible.

Whilst Mr Justice Birss found this patent to be invalid for both implausibility and obviousness, he refused to examine the extent to which the standard for plausibility differed from the standard for obviousness in this case. However, this point was considered by Mr Justice Carr in a case where Actavis sought revocation of Lilly's patent relating to the second medical use of tomoxetine for the treatment of ADHD[47]. The specification contained no experimental data but disclosed the mechanism of action of tomoxetine as a selective noradrenaline (norepinephrine) reuptake inhibitor. Mr Justice Carr stated that "there is no requirement in the EPC that a patent should contain data or experimental proof to support its claims". Mr Justice Carr drew a line between claims of wide scope, such as those dealt with in *Salk*, where experimental data may well be required to make the claimed invention plausible and claims of narrow scope, such as those in issue in *Actavis*, where such data may not be required. As such, the reference in *Salk* to the need for experimental tests to support the claimed therapeutic use could be distinguished and, in any case, the exact wording in *Salk* – "for example, experimental tests" – did not suggest that experimental tests were the benchmark that had to be reached for the specification to be plausible. Therefore, despite the absence of any data, the patent, as read in light of the common general knowledge of the skilled clinician, was found plausible because it was 'reasonable' that the disclosed mechanism of action of tomoxetine as a selective norepinephrine reuptake inhibitor could be used to treat ADHD.

To answer the question left unanswered by Mr Justice Birss, Mr Justice Carr explained that:
"the standard for assessment of plausibility is not the same as assessment of obviousness. For obviousness, a fair expectation of

success is required because, in an empirical art, many routes may be obvious to try, without any real idea of whether they will work. The denial of patent protection based upon the "obvious to try" criterion alone would provide insufficient incentive for research and development in, for example, pharmaceuticals and biotechnology, and would lead to the conclusion that a research program of uncertain outcome would deprive a patent of inventive step. The reason why the court requires that the invention of a patent should be plausible is different. It is to exclude speculative patents, based on mere assertion, where there is no real reason to suppose that the assertion is true."

The approach of Mr Justice Carr was also endorsed by Mr Justice Birss in the subsequent case of *Actavis v ICOS*[48]. Therefore, it can be seen that "plausibility is a relatively low threshold," as stated by Mr Justice Arnold in *Mylan v Warner-Lambert*[49], an approach confirmed by the Court of Appeal in their decision in the same case. In his judgment, Lord Justice Kitchin summarised the nature of the threshold, and the fact that it is lower than the reasonable expectation of success for obviousness, as follows: *"46. The EPO and domestic cases do, however, indicate that the requirement of plausibility is a low, threshold test. It is designed to prohibit speculative claiming, which would otherwise allow the armchair inventor a monopoly over a field of endeavour to which he has made no contribution. It is not designed to prohibit patents for good faith predictions which have some, albeit manifestly incomplete, basis. Such claims may turn out to be insufficient nonetheless if the prediction turns out to be untrue. A patent which accurately predicts that an invention will work is, however, not likely to be revoked on the ground that the prediction was based on the slimmest of evidence. Thus, the claims will easily be seen not to be speculative where the inventor provides a reasonably credible theory as to why the invention will or might work. The same is true where the data in the specification is such that the reader is encouraged to try the invention.*
47. We heard argument as to whether the invention is only to be treated as plausible if the reader of the specification would be encouraged to try the invention with a reasonable prospect of success, thereby bringing the test for plausibility into line with that sometimes used in the context of obviousness. I do not accept that there is any reason to align the tests in this way. A test designed to prevent speculative claiming need go no further than requiring the patentee to show that the claim is not speculative: the specification does not need to provide the reader with any greater degree of confidence in the patentee's prediction than that."

Mr Justice Birss considered plausibility again in a case where Merck sought revocation of Ono's patent relating to the use of anti-PD-1 antibodies for the treatment of cancer on a number of grounds, including, in relation to sufficiency, that the patent did not render it plausible that all cancers could be treated by the claimed antibodies[50]. Additionally, Merck argued that the patent was insufficient because it presented an unduly burdensome research program to find an anti-PD-1 antibody which is suitable to treat all cancers and that the scope of the claims were wider than the patent's technical contribution since Merck were able to show that the claimed invention did not provide any therapeutic effect in relation to a number of specific types of cancer, so that no principle of general application had in fact been disclosed.

In relation to plausibility in the context of sufficiency, Mr Justice Birss cautioned against applying previous case law too strictly, stating that *"whenever one is considering plausibility it must be done in the context of the invention determined by properly construing the claim and one must keep in mind the particular legal objection which is under consideration."* Mr Justice Birss came to this conclusion after comparing the present case with that of *Human Genome Sciences* (HGS). In *HGS,* the court set a low standard for plausibility in relation to product claims. In contrast, Ono's submission that a higher standard of disclosure may be required to establish the plausibility of Swiss-style and EPC 2000 type claims, was accepted. Specifically in relation to purpose-limited medical use claims, Mr Justice Birss held that *"the material relied on to establish plausibility must be both sufficiently specific, and have a sufficient breadth of application, to fairly support the claim both in terms of the nature of the agent claimed to have an effect, and in terms of the effect claimed."*

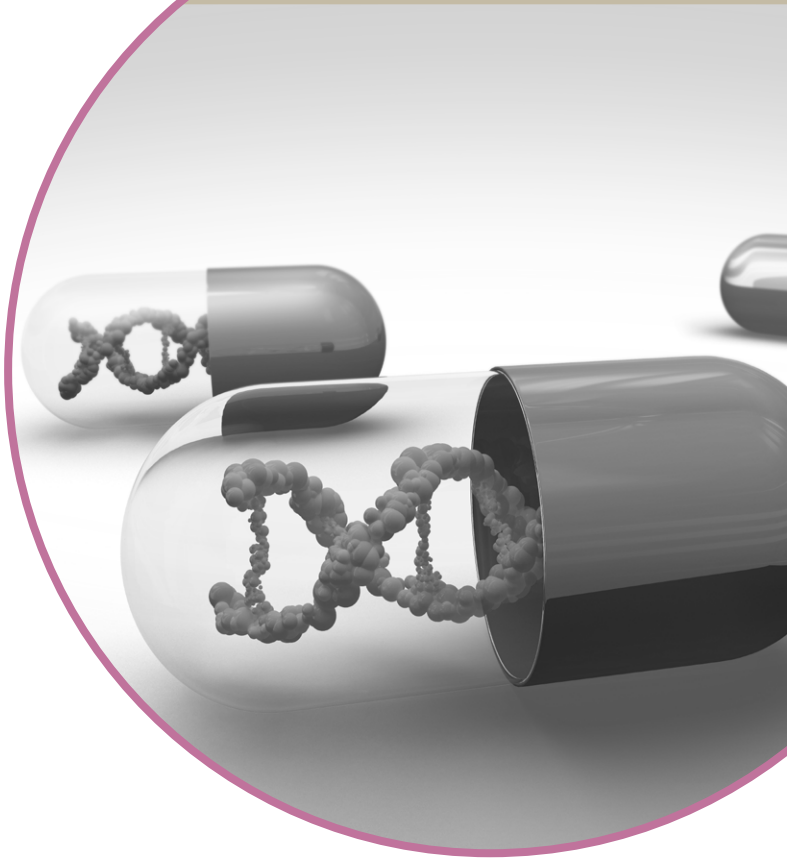
Ono's patent contained in vivo mouse data which showed that the claimed antibodies exhibited their effect on cancer by boosting the immune system's ability to respond to the cancer in question. Mr Justice Birss held that this evidence provided a principle of general application such that the skilled person would be able to make a "reasonable prediction that the therapy will work to treat cancer." Therefore, despite the fact that the treatment would not be a "success in every patient in all circumstances," the specification was held to make the invention plausible across the scope of the claim.

Future perspective

In light of the two leading Court of Appeal judgments on the point (*Regeneron v Genentech* and *Warner-Lambert v Mylan*) it appears fairly settled that the hurdle for plausibility, at least in terms of sufficiency, is not as high as many feared it had become. The authors hope that a relatively low threshold test for plausibility continues to be applied by the court going forward given that new research, particularly into new medical uses of existing pharmaceuticals, needs to be encouraged in light of the difficulties that currently face the pharmaceutical industry in the identification of new chemical compounds suitable for drug development. Furthermore, the authors suggest that a low threshold is appropriate given that plausibility is neither a statutory requirement of the Patents Act 1977 nor the EPC. It will also be interesting to observe how the approach to the question of plausibility is developed in relation to other grounds of invalidity. For example, in the recent *Idenix v Gilead* case the Court of Appeal also considered the question of plausibility as it applied to the technical effect underlying a claim for inventiveness, which revisits the approach of the EPO when it initially introduced the concept under the problem and solution approach to inventive step. In that case, Lord Justice Kitchin held that "the same approach should be adopted in considering obviousness and whether a technical effect is plausible in the light of the teaching in the specification and the common general knowledge. There must be a real reason for supposing that the claimed invention will indeed have the promised technical effect." Whether this will lead to a greater alignment of the English approach to inventive step with that of the EPO in cases where plausibility is in issue remains to be seen.

33 Human Genome Sciences v Eli Lilly [2012] RPC 6
34 Actavis v Eli Lilly [2015] EWHC 3294 (Pat)
35 AgrEvo (T 0939/92)
36 Johns Hopkins (T 1329/04)
37 Conor Medsystems v Angiotech [2008] RPC 28
38 Section 72(1)(c) Patents Act 1977
39 Biogen v Medeva [1997] RPC 1
40 Regeneron v Genentech [2013] EWCA Civ 93
41 Idenix v Gilead [2014] EWHC 3916 (Pat)
42 Warner-Lambert v Generics (UK) Ltd (t/a Mylan) [2016] EWCA Civ 1006
43 Idenix v Gilead [2016] EWCA Civ 1089
44 per Regeneron v Genentech [2013] EWCA Civ 93
45 Salk (T 0609/02)
46 Hospira v Genentech [2014] EWHC 1094 (Pat)
47 Actavis v Eli Lilly [2015] EWHC 3294 (Pat)
48 Actavis v ICOS [2016] EWHC 1955 (Pat)
49 Generics (UK) Ltd (t/a Mylan) v Warner-Lambert [2015] EWHC 2548 (Pat)
50 Merck Sharpe & Dohme v Ono [2015] EWHC 2973 (Pat)

Regulatory



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A risk based approach to Good Manufacturing Practice for Advanced Therapy Medicinal Products?

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On 28 June 2016, the European Commission's Directorate General for Health and Food Safety issued a targeted stakeholder consultation on its draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products (the "Guidelines").

The deadline for responses was 26 September and on the 2 December the Commission published a summary of the responses. Responses have been submitted by 53 contributors including stakeholders involved in the development, manufacture and / or commercialisation of advanced therapy medicinal products ("ATMPs"), SMEs and academia.

The draft Guidelines have been issued pursuant to Article 5 of Regulation 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC (the "ATMP Regulation"), which requires the Commission to draw up guidelines on Good Manufacturing Practice (GMP) specific to ATMPs.

The Commission has taken into account its previous consultation exercise on GMP Guidelines for ATMPs which ran from July to November 2015. The 2015 consultation saw responses from 48 stakeholders from academia, industry (including SMEs) and others, as well as input from the European Medicines Agency (EMA) and Member State competent authorities. This consultation gives an additional opportunity for concerned stakeholders to express their views prior to the Commission finalising the Guidelines.

What is an ATMP?

According to Article 2(1)(a) of the ATMP Regulation, an ATMP is any of the following medicinal products for human use:

- A gene therapy medicinal product - a biological medicinal product with the characteristics defined in Part IV of Annex I to Directive 2001/83/EC as amended (the "Directive")
- A somatic cell therapy medicinal product - a biological medicinal product with the characteristics defined in Part IV of Annex I to the Directive
- A tissue engineered product as defined in Article 2(1)(b) of the ATMP Regulation

A procedure to determine the classification of borderline products is provided in Article 17 of the ATMP Regulation and further guidance on the classification of ATMPs is contained in the EMA's Reflection Paper on the Classification of ATMPs (last updated in June 2015).

The draft GMP Guidelines

The draft Guidelines issued this June are twice the length of the draft issued in 2015, clearly seeking to address certain comments requesting more detail on particular topics. Interestingly, in 2015 around 20% of contributors (more commonly industry) had a negative perception of the development of a self-standing guideline, with some comments appearing to be based on the perception that the intention is to create double standards for industry vs academia/hospitals.

This article focuses on the risk-based approach to GMP for ATMP which is detailed in the Guidelines, although of course the Guidelines deal with many other aspects of GMP including all the expected elements such as production, documentation, testing, batch release etc., and some elements more specific to ATMPs such as seed lot and cell bank systems, environmental control measures, re-constitution after batch release and automated production.

The risk-based approach

The 2015 draft introduced the concept of a risk-based approach to GMP for ATMPs, to take account of the fact that due to the

complexities of ATMPs, the risks may differ according to the type of product, the nature/characteristics of the starting materials and the level of complexity of the manufacturing process, as well as the fact that manufacturing of autologous ATMPs poses specific challenges meaning that quality strategies should be tailored to the constraints of the manufacturing process and of the product in practice. The Guidelines recognise the importance of flexibility in the application of GMP, to allow manufacturers to implement the measures that are most appropriate having regard to the specific characteristics of the product itself and the manufacturing process. As expected there was strong support for this risk-based approach in the 2015 consultation responses, although the majority of responders asked for additional guidance as to how this approach would be applied in practice (and whereas the 2015 draft dedicated one page to this concept, the 2016 draft dedicates five and a half).

The 2016 draft Guidelines explicitly state that the risk-based approach is applicable to all types of operators in an equal way, regardless of the setting in which they are developed (presumably as an attempt to address the concerns that there may be double standards for industry vs academia). They also emphasise that whilst the risk-based approach brings flexibility, it also implies that additional measures may be needed if necessary to address specific risks relating to the nature of the product / manufacturing process. The level of effort and documentation should be commensurate with the risk.

A distinction is drawn between investigational ATMPs and authorised ATMPs. Additional waivers/flexibilities may be possible in early phases of clinical trials, but as the trials become more advanced the manufacturing and control methods are expected to become more detailed and refined. However, the Guidelines highlight that an immature quality system may compromise the use of the study in a marketing authorisation ("MA") application, or the approval of the clinical trial. Manufacturers are strongly encouraged to take advice from the competent authorities on the use of a risk-based approach for investigational ATMPs. For authorised ATMPs it may be possible to deviate from standard expectations within the content of the MA application, again provided that this can be adequately justified, and for aspects not covered by the MA, the manufacturer must document the reasons for a risk-based approach, justifying that the measures applied are adequate to ensure the quality of the product.

Examples of the application of the risk based approach are given in the Guidelines, including in relation to ensuring the quality of raw materials and release testing strategies.

Summary

This article has focused on just one element of the draft Guidelines, but one that is fundamental to the GMP approach to be taken by developers/manufacturers of ATMPs. Once the Guidelines are finalised, if use of the risk-based approach is proposed, it will be essential that the safety and quality of the ATMP can be fully justified and documented. It will be highly advisable to consult with the competent authorities as the consequences of taking the wrong approach could be significant - a delay in the granting of an MA or the inability to conduct a clinical trial in the matter proposed. It will also be reasonable to expect that Post Approval or Risk Management Plan measures in relation to manufacturing may be imposed by the EMA to address issues regarding the manufacture of ATMPs in particular where the risk based approach is used. Clarity would also be helpful in relation to how existing GMP guidelines (e.g. EudraLex Volume 4, Annex 2 (biological active substances and medicinal products)) will fit alongside these Guidelines.

The consultation responses are generally favourable towards the risk-based approach. However concerns were raised by a significant number of stakeholders regarding other aspects of the Guidelines such as QP certification, premises and aseptic manufacturing. The format of the document (a standalone document verses an annex of Volume 4) was also a comcern, with stakeholders seeking certainty on the application of the remainder of Eudralex Volume 4 to ATMPs. The Commission's response and the next version of the Guidelines are eagerly awaited.

Navigating EU Pharmaceutical Law edited by Maria Isabel Manley and Marina Vickers

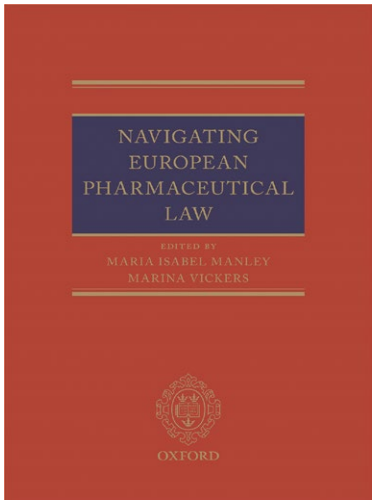
The law and regulation relevant to the development, marketing, and protection of a bio/pharmaceutical product is sprawling and diverse; more a 'landscape' than a 'framework'.

This situation is exacerbated by the fact that Member States have retained their prerogatives to regulate in some areas, such as in relation to pricing and reimbursement of a medicinal product, which results in a 'patchwork' of different regimes that bio/pharmaceuticals companies need to master to ensure an effective and efficient penetration of the single market that is the European Union.

This book aims to guide its readers through the legal and regulatory landscape applicable to bio/pharmaceutical products in the European Union. It provides a detailed analysis of the relevant law and regulation, and scrutinises issues of controversy or uncertainty.

A core part of this book examines and analyses the intellectual property 'regulatory' rights which may be applicable to a bio/pharmaceutical product, with individual chapters devoted respectively to: regulatory data protection, supplementary protection certificates, orphan market exclusivity, and the rewards available under the paediatric legal framework. A separate chapter on the maximisation of rights illustrates key issues and legal controversies by way of a detailed case study.

If you would like to purchase this book, please visit the Oxford University Press website or contact marie.manley@bristows.com for more details. We have the pleasure of donating any royalties derived from this book to the Great Ormond Street Hospital Charity.



Biosimilars: an overview

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The full version of this article appears as part of a LexisNexis Practice Note.

What is a biosimilar?

A similar biological medicinal product (commonly termed 'biosimilar') is a medicinal product that is similar to a biological medicinal product (**the originator product)** that has already been granted a marketing authorisation in the EU/EEA, but which does not meet the definition of a generic medicinal product owing, in particular, to differences in raw materials or manufacturing processes. In the United States (**US**), biosimilars are often termed 'comparable biologics' or 'follow-on biologics'. The US has defined the term 'Interchangeable Biological Product' which generally requires a higher standard of interchangeability than in Europe. Since the originator product (also known as the 'reference product') is a biological medicinal product, it is also necessary to understand what constitutes a biological medicinal product.

What is a biological medicinal product?

The legal definition of 'biological medicinal product' is set out at section 3.2.1.1 (b), Part I, Annex I of Directive 2001/83/EC, as amended (the **Community Code on Medicinal Products**), as follows:

"A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation 2309/ 93[51]*; advanced therapy medicinal products as defined in Part IV of this Annex"*

Consequently, a medicinal product will be classed as a biological medicinal product if the active substance is biological, namely, a substance that:

- is produced by or extracted from a biological source; and
- needs for its characterisation and the determination of its quality a combination of physico–chemical–biological testing, together with the production process and its control.

In addition, the legal definition set out above provides for categories of products that will automatically qualify as a 'biological medicinal product', as follows:

- **Immunological medicinal products and medicinal products derived from human blood and human plasma.** Article 1(4) of the Community Code on Medicinal Products defines 'Immunological medicinal products' as: *"Any medicinal product consisting of vaccines, toxins, serums or allergen products: (a) vaccines, toxins and serums shall cover in particular: (i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine; (ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin; (iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin; (b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent".* Article 1(10) of the Community Code on Medicinal Products defines 'Medicinal products derived from human blood or human plasma' as: 'Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin'.

- **Medicinal products developed by means of one of the following biotechnological processes**: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods (defined in section 1 of the Annex to the EMA Regulation),and

- **Advanced therapy medicinal products** (defined in Article 2(1) of Regulation (EC) 1394/2007)

Scientific background of biosimilars

Biological active substances are large and complex molecules in comparison to the chemical active substances found in traditional medicinal products.

For traditional medicinal products, once the relevant periods of intellectual property and regulatory data protection for the reference product have expired, generic companies will often manufacture medicinal products that have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product. These are the so-called 'generics'. In this scenario, the generic company simply refers to the dossier of the reference product in order to evidence the safety and efficacy of its generic product. Generally, the only additional data required from the generic company is that from appropriate bioavailability studies, in order to demonstrate bioequivalence of the generic product with the reference product.

However, the situation is different for biological medicinal products. Due to the complexity of biological medicinal products and complicated manufacturing processes, it is never possible to produce an identical version of a biological medicinal product. Indeed, a biosimilar can only be shown to be similar but not identical to the originator product. To that end, comparability studies are required to evidence the similar nature, in terms of quality, safety and efficacy, of the biosimilar to the chosen reference biological medicinal product authorised in the EU/EEA. Commonly, these will require clinical trials data.

EU regulatory framework for biosimilars

This section addresses the legal basis and the procedure for obtaining a marketing authorisation for a biosimilar in the EU. The EU regulatory framework for medicines was not originally designed with biosimilars in mind, and hence an applicable regulatory approval pathway was lacking. This issue was brought to the fore by Sandoz' application for the approval of its biosimilar Omnitrope (somatropin), which was eventually approved on 12 April 2006. Sandoz' initial application for Omnitrope was based on Article 10(a) (previously Article 10(1)(a)(ii)) of the Community Code on Medicinal Products, which provides a procedure for 'bibliographic' applications based on well established medicinal use. However, despite a positive assessment by the European Medicines Agency (**EMA**) in 2003, the European Commission refused to authorise Sandoz' initial application on the basis that this chosen legal pathway was not suitable for biosimilars. Following this, Directive 2004/27/EC amending Directive 2001/83/EC introduced a specific regulatory pathway for biosimilars, which is described below.

Legal basis for a biosimilar marketing authorisation in the EU

The legal basis for biosimilar applications can be found in Article 10(4) of the Community Code on Medicinal Products, which provides that:

"'where a biological medicinal product that is similar to a reference biological medicinal 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. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided."

The requirements for a marketing authorisation application (or 'dossier') for a biosimilar are found in section 4, Part II, Annex I of the Community Code on Medicinal Products. Since a biosimilar is not identical to its reference biological medicinal product, the toxicological and clinical profile of the biosimilar must be included in the dossier. The type and amount of such additional data (e.g. toxicological and other non-clinical and appropriate clinical data) is determined on a case-by-case basis in accordance with the relevant scientific guidelines.

The EMA Guideline on similar biological medicinal products states that in specific circumstances, a confirmatory clinical trial may not be necessary. It does, however, require that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and pharmacodynamic and/or pharmacokinetic profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to con-cern. Since the matter is to be determined on a case by case basis, it is recommended that applicants discuss the option of using this simplified approach with the regulatory authorities.

It is also important to note that a single reference biological medicinal product, defined on the basis of its marketing authorisation in the EU, should be used as the comparator throughout the comparability programme for quality, safety and efficacy studies during the development of a biosimilar, in order to allow the generation of coherent data and conclusions. There are limited exceptions to this position.

Procedure to obtain a marketing authorisation in the EU

Often, biosimilars will:

- be produced by one of the following biotechnological processes: recombinant DNA technolo-gy; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; or hybridoma and monoclonal antibody methods, and/or
- qualify as an advanced therapy medicinal product

Where this is the case, the biosimilar will fall into the mandatory scope of the centralised approval proce-dure as provided by Article 3(1) of the EMA Regulation. This means that it must be approved by the Com-mission on the basis of a positive opinion from the EMA, as opposed to a national competent authority in the EU.

Other products that fall within the mandatory centralised approval procedure include medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treat-ed animals or to increase yields from treated animals; medicinal products for human use containing a new active substance intended to treat certain diseases (acquired immune deficiency syndrome, cancer, neuro-degenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions, viral diseases); and medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) 141/2000 on orphan medicinal products.

If the mandatory scope of the centralised approval procedure does not apply then the biosimilar would fall within its optional scope, meaning that authorisation by a national competent authority would be an option. Biosimilar marketing authorisation applications for which the reference product is a biological medicinal product authorised via the centralised procedure have automatic access to the centralised procedure under Article 3(3) of the EMA Regulation.

Difficulties in manufacturing biosimilars

In contrast to small molecule generic drugs, biosimilars are difficult to manufacture because of the complex-ity of the biological products and the sensitivity of the products to the manufacturing process. Moreover, the particular cell line from which the reference product is derived is not available to a biosimilar manufac-turer. Inevitably, therefore, biosimilars will not be identical to the reference product. For example, they may have different glycosylation features and the purification and formulation steps will also lead to differences in the final product. As a result, further data will be required to demonstrate the required level of similarity for regulatory purposes.

While the data requirements for a biosimilar application far outweigh those for a traditional generic medicinal product, the establishment of a regulatory pathway for the approval of biosimilars has successfully facilitat-ed the entry (although not a flood) of these medicinal products to the market. As of July 2016, 24 biosimilar applications have been reviewed by the EMA leading to 20 approvals, two withdrawals of the applications, and two refusals (for further information see the EMA website). The concerns of the EMA expressed in rela-tion to the refused applications were mainly related to a lack of sufficient data to evidence comparability to the reference product and failure to adequately define the manufacturing process.

Pharmacovigilance monitoring

All medicinal products are carefully monitored after they are placed on the EU market in order to continually assess the safety profile of that product. This process is termed 'pharmacovigilance'. All biological medici-nal products, including biosimilars, authorised after 1 January 2011 are subject to additional pharmacovigi-lance monitoring (Article 23 of Regulation (EU) 1235/2010 and Article 11 of Directive 2010/84/EU). This means that they are monitored particularly closely by regulatory authorities.

Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and in the information for healthcare professionals, together with a short sentence explaining what the triangle means i.e. 'this medicinal product is subject to additional monitoring'.

In order to support pharmacovigilance monitoring and in accordance with Article 102(e) of the Community Code on Medicinal Products, the EMA has stated that all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number (see Guideline on similar biological medicinal products on the EMA website).

A marketing authorisation holder for a biosimilar must make a significant investment in its post-marketing pharmacovigilance system. This is of particular importance for biological medicinal products because a change in the manufacturing process may lead to an otherwise undetected change to the safety profile of the product.

Market access

Some issues posed by biosimilars, such as pricing, reimbursement and interchangeability, remain the prerogative of the national competent authorities of the Member States and not the EMA.

In relation to pricing and reimbursement, the cost of a biosimilar will be lower than the cost of the originator product due to comparably reduced development costs. The biosimilar will therefore serve as an attractive treatment option from the perspective of the payer in terms of cost. However, one major hurdle to the up-take of biosimilars is the issue of interchangeability, namely, the clinical feasibility of switching a patient's treatment plan from the originator product to the biosimilar.

The EMA has made clear that decisions on interchangeability and/or substitution regarding the reference biological medicinal product and a biosimilar rest with national competent authorities and are outside the remit of EMA. In the UK, the position of the Medicines and Healthcare product Regulatory Agency (**MHRA**) is that a biosimilar product is not presumed to be identical to the originator product. Hence, prescribers of biological products are advised to use the brand name in order to prevent automatic substitution for the biosimilar when the medicine is dispensed by the pharmacist[52].

Guidance documents

The following guidelines of the EMA should be taken into account by companies preparing to submit a mar-keting authorisation application for a biosimilar:

- Guideline on similar biological medicinal products (EMA/CHMP/437/04/2014 Rev. 1)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)

Specific product related guidelines can be found on the EMA website.

There are also various other guidelines related to biosimilars available on the EMA website.

National guidelines should also be consulted where they exist. In the UK, the MHRA has issued a Drug Safety Update on Biosimilar Products. This refers to the EMA guidelines.

While guidance is not legally binding, the competent authorities will generally expect applicants to have complied with all applicable guidance, unless otherwise justified.

US Food and Drug Administration procedures regarding The 'Bolar-type exemption'

The 'Bolar-type exemption' is how the provision in paragraph 6 of Article 10 of the Community Code on Me-dicinal Products is often referred to and it provides that:

'"Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplemen-tary protection certificates for medicinal products."

In other words, conducting the necessary studies and trials to gain regulatory approval for generic or biosimilar products will not constitute a patent infringement, which is particularly important for biosimilars where additional clinical trial data may be required to achieve regulatory approval.

Its implementation differs in different EU countries. Some take a narrow view of what falls within the exemp-tion while others take a broader view. In the UK, it has been implemented by section 60(5)(i) of the Patents Act 1977 (**PA 1977**), which expressly refers to paragraphs 1–4 of Article 10 and therefore only applies to biosimilars for which regulatory approval is sought with a view to the application of paragraphs 1–4.

In the UK the experimental use exemption at PA 1977, s 60(5)(b) also (now) provides some additional com-fort to parties who wish to undertake acts which would potentially otherwise constitute an infringement of a patent. It provides an exemption from infringement if the act 'is done for experimental purposes relating to the subject-matter of the invention'. This was originally interpreted by the courts to apply narrowly and so did not include certain studies and trials done for regulatory purposes. However,

it has been broadened by the addition of ss 6D–6G and now explicitly applies to: 'anything done in or for the purposes of a medicinal product assessment' (s 6D). This includes anything done for the purposes of obtaining or varying an author-isation (s 6E(a)) or complying with a regulatory requirement in relation to such an authorisation (s 6E(b)) anywhere in the world, not just in the UK. As a result, there is less chance of a biosimilar manufacturer falling between the 'cracks' between section 60(5)(b) and (i).

The reason that the EU exemption is called the 'Bolar-type' exemption is because of the US case of *Roche Products v Bolar Pharmaceutical* (733 F.2d 858 (Fed. Cir. 1984)) which led to the a US 'safe harbor' provision in section 271(e)(1) of the Drug Price Competition and Patent Terms Restoration Act 1984 (the 'Hatch-Waxman' Act). The 'safe harbor' is for infringement from liability for acts reasonably related to the development and submission of any information to the FDA. It has been held to apply to medical devices and there is no suggestion that it should not be understood equally to cover biosimilars.

As long as the trials fall within the Bolar-type exemption, the timing of scheduling of the clinical trials are not affected.
It is interesting to point out that clinical trials aimed to purely compare products to support health technology assessment applications will not *stricto sensu* fall within the scope of the Bolar-type exemption as such trials are not usually required to obtain regulatory approval but are necessary in order to get effective access to the market. Nevertheless, they fall within the wider scope of the UK experimental use exemption introduced by section 6D PA 1977.

51 Regulation (EU) 2309/93 has been repealed by Regulation (EC) 726/2004 laying down Community proce-dures for the authorisation and supervision of medicinal products for human and veterinary use and estab-lishing a European Medicines Agency (the EMA Regulation)
52 see MHRA Drug Safety Update, Biosimilar Products, 1 February 2008

"...conducting the necessary studies and trials to gain regulatory approval for generic or biosimilar products will not constitute a patent infringement"

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Trends in Biotech financing: 2016 signals a continuing trend towards more significant funding rounds directed at fewer, better positioned companies

Nick Cross
Associate
Bristows LLP

The Biotechnology sector has enjoyed strong performance and ready access to capital over the past few years; nowhere is this more clearly visible than in the performance of the NASDAQ Biotech Index which reached an all-time high in 2015. Similarly, 2015 represented a record breaking year for the British Biotech industry with £489m of VC funding raised over the course of the 12 month period[53]. However, Biotech financing slowed markedly towards the end of 2015 and sector performance in 2016 has reflected a more cautious approach from investors.

Equity Capital Markets

Political uncertainty on the wider global scale, including the UK referendum on EU membership and the US Presidential election campaign, has seen a widely acknowledged decline in IPOs in the Biotech industry in 2016. With there being no current settled timetable for "Brexit" negotiations between the UK and EU, many of the wider macroeconomic factors behind this trend are set to continue and, as such, 2017 may not be a bumper year for Biotech IPOs.

Many Biotech companies achieving IPOs recently have failed to impress investors, and the market environment is becoming tougher for new entrants. It is not all doom and gloom however;

both Shield Therapeutics and Mereo Biopharma made successful listings on AIM in February and June 2016 respectively, while GeNeuro, a Swiss Biotech focussing on autoimmune diseases, listed on the Paris Euronext in April, demonstrating continued appetite from European capital markets.

One of the most interesting developments noted by the industry throughout 2015 and 2016 is the significant rise in the level of follow-on funds raised by already listed Biotechs. Follow-on funds accounted for over 60% of the total amount raised by Biotech companies on the London Stock Exchange during 2015[54], demonstrating the continued value of access to public markets after initial public offerings.

Private Financing and Venture Capital

While public market performance has been underwhelming, particularly in Europe, venture funding in the latter half of 2015 and in 2016 has performed well. There has also been a move towards larger financing rounds of fewer but perhaps better positioned businesses.

Investors appear to be less inclined to adopt the traditional "drip-feed" method of funding, with larger sums being invested early-on to allow companies to forge ahead with product development and with the aim of securing a safer, early exit. An example of this trend is Carrick Therapeutics securing $95m in funding commitments in October 2016[56].

At the other end of a company's lifecycle, figures for the first part of 2016 saw a slight reduction of reported seed capital funding for fledgling Biotech companies. It is hoped that the policies of the current conservative government will build on schemes such as R&D tax credits, the Enterprise Investment Scheme, the Seed Enterprise Investment Scheme and the Patent Box, as well as the incoming Investors' Relief, in order to give a further boost to this crucial area of the industry.

Crowdfunding

Perhaps one of the most eye-catching trends in Biotech financing to look out for is the continued growth of Biotech crowdfunding. This alternative source of funding represents another option for fledgling companies, which are increasingly turning to platforms such as SyndicateRoom or Title III crowdfunders in the US in the search for new investors. By way of example, Apta Biosciences, a research tool company based in the UK and Singapore, has raised £2.8m in two separate rounds with SyndicateRoom. In April 2016, AIM-listed Scancell took things one step further by using the same platform to crowdfund part of a £6.1m share placing, giving retail and institutional investors an equal footing. Whether the Biotech sector can attract significant levels of crowdfunding in the long term, however, remains to be seen.

Conclusion

Biotech companies looking to raise funds in 2016 have faced challenging global economic conditions. Despite these conditions, appetite for investment in Biotech companies, and in particular private financings, remains strong - PwC have recently reported that in the third quarter of 2016 the Biotechnology sector received the second largest amount (by sector) of venture capital funding[55] – fuelled by commercial interest in potentially transformational areas of research such as CRISPR gene-editing technology and synthetic drug development.

53 BIA – UK Biotech financing and deals in 2015/16 – Money, momentum and maturity. June 2016
54 BIA – UK Biotech financing and deals in 2015/16 – Money, momentum and maturity. June 2016
55 http://www.pwc.com/us/en/health-industries/pharma-life-sciences/publications/pharma-life-sciences-deals-insights.html
56 http://www.bristows.com/news-and-publications/press-coverage/oncology-start-up-carrick-attracts-95m-funding/

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Tax developments in 2016

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UK patent box changes

Following complaints by Germany to the EU Commission and a report by the OECD's Forum on Harmful Tax Practices (FHTP), HM Treasury announced that the UK patent box would be amended. The FHTP identified the patent box as potentially harmful and the general consensus seemed to be that it was insufficiently targeted and had inadequate links with the R&D activity that eventually resulted in profits being generated. It was argued that it was a 'harmful' measure designed to attract business to the UK rather than a legitimate reward for innovation.

The government also confirmed that it would make the patent box BEPS-compliant (i.e. to satisfy the requirements of the reports on Base Erosion and Profit Shifting produced by the OECD) by making the low (10%) tax rate dependent on, and proportional to, the extent of R&D expenditure incurred by the company claiming the relief. This change come into effect on 1 July 2016.

The new regime is based on the OECD's "modified nexus approach" (MNA) – this approach seeks to ensure that preferential IP regimes require substantial economic activities to be undertaken in the jurisdiction in which the regime exists and that tax benefits are connected directly to R&D expenditure.

The amendments closed the existing UK regime to new entrants (products and patents) in June 2016 and the existing regime will be abolished by June 2021. To allow transition to the new regime, IP within the existing regime will retain the benefits of that regime until June 2021.

The amendments to the regime also make 'streaming' mandatory. This is a process by which the profits that relate solely to a particular patent are isolated from the total profits made by a company. Previously it was possible to do this on a company-wide basis, but now it must be done on a patent-by-patent or product-by-product basis, which for some companies will make the compliance process considerably more onerous.

UK withholding tax changes

Budget 2016 brought a number of unexpected tax changes. One change that could have an impact on the life sciences sector is a proposed change to the UK withholding tax regime on royalties.

Withholding tax is UK tax that the royalty payer (licensee) must withhold from its payment to the royalty recipient (licensor) and pay to HMRC as a sort of 'down payment' on the licensor's UK tax liability on the royalty. Most countries operate a similar regime. It is levied at 20% in the UK on royalties for patents (and also for other IP rights such as copyright and design rights in certain situations). With effect from Royal Assent to the Finance Bill (which occurred in mid-September 2016 and created the Finance Act 2016), withholding tax will also apply to royalties for trade marks and trade names.

The change will not affect current patent licences (unless they include a trade mark licence), but it could affect licences for branded non-patent protected items (such as a branded, off-patent drug). Currently, payment of a royalty for a trade mark licence for an off-patent drug would not be subject to withholding tax in the UK, but this is changed by the Finance Act 2016.

The Finance Act 2016 also prohibits group companies (or other connected parties) from accessing the benefits of double tax treaties (which can reduce or eliminate withholding tax) if trying to access those benefits forms part of a tax avoidance arrangement.

The practical consequence of these measures is that parties to licences of (or which include) trade marks or trade names where there is a UK licensee will need to think more carefully about the withholding tax position and make sure their licences include withholding tax provisions, if they do not already. This is to ensure that each party knows what the result of a withholding might be (for example, the UK licensee might be required to gross-up the payment to counteract the effect of the withholding) and whether any relevant double tax treaty between the UK and the jurisdiction of the licensor can be used to alleviate the situation (for example, by reducing or eliminating the requirement to withhold).

Competition

Our competition practice

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.

Genentech CJEU decision: royalties despite revocation or non-infringement permitted under EU competition law

Helen Hopson
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Licence royalty structure is a particularly important issue in the Biotech industry owing to the prevalence of agreements entered into early in the drug development process and resultant lags in commercialisation and revenue generation. Royalty terms where regular payments are reduced but cover an extended period, or where payments ratchet up once regulatory milestones have been met can be attractive particularly where the rewards of commercialisation are uncertain.

The Court of Justice of the European Union ("CJEU") has confirmed in a recent Biotech case[57] that an obligation to pay running royalties under a patent licence cannot be avoided on competition law grounds, even though the underlying patent(s) have been revoked or are held not to have been infringed, provided the licence may be terminated upon reasonable notice by the licensee. This builds on existing EU case law that it is not anti-competitive in the EU for parties to agree to a royalty term that continues even after the licensed Intellectual Property Rights ("IPRs") have expired. The decision will largely be welcomed by the Biotech industry as it permits greater flexibility in the commercial terms of deals which should help stimulate R&D and licensing. However, given that much drug development takes place globally, parties should also be aware of the differing position in the US (and possibly other jurisdictions).

Background to the case

The case arises from a worldwide, non-exclusive patent licence, granted by Behringwerke to Genentech in 1992, for the use of a human cytomegalovirus ("HCMV") enhancer to improve the effective synthesis of recombinant proteins in the production of rituximab (a monoclonal antibody commonly used to treat non-Hodgkin lymphoma and rheumatoid arthritis). The licence, governed by German law and containing an arbitration clause, required the payment of various fees including a running royalty levied on the amount of 'finished products' sold. The licence concerned one European patent and two US patents. In 1999, the European Patent Office revoked the European Patent, but the two US patents remained in force throughout the term of the agreement.

In 2008, Genentech terminated the agreement following a request from Hoechst (the successor company to Behringwerke) for information about the number of finished products Genentech had sold. Hoechst believed that Genentech had been using the HCMV enhancer for the production of its product Rituxan®/MabThera® (active ingredient rituximab). Notwithstanding Genentech's termination of the agreement, Hoechst launched arbitration proceedings claiming payment of royalties in respect of the 'finished products' sold by Genentech before termination. Meanwhile, Genentech and Biogen brought an action for revocation of the US patents in US proceedings commenced by Hoechst, but the revocation action failed and the appeal against that decision was dismissed.

In September 2012, the arbitrator held that the commercial purpose of the licence was to avert all litigation on the validity of the patents, and as such, the outcome of the 1999 opposition proceedings before the EPO did not release Genentech from its obligation to pay the royalties under the European patent.

Genentech appealed the decision to the Paris Court of Appeal seeking an annulment on the basis that the arbitrator's interpretation of the licence put Genentech at a competitive disadvantage compared to competitors who had not been

required to pay for the IP relating to the HCMV enhancer, and therefore violated Article 101(1) of the Treaty on the Functioning of the European Union ("TFEU"). The Court of Appeal subsequently referred a question to the CJEU for a preliminary ruling on whether Article 101(1) TFEU should be interpreted as precluding effect being given, where patents are revoked, to a licence which requires the licensee to pay royalties for the sole use of the rights attached to the licensed patent.

Advocate General's opinion

In line with standard procedure on preliminary references to the CJEU, Advocate General (AG) Wathelet gave an opinion on the issues before the CJEU reached its judgment. The Advocate General interpreted the Court of Appeal's question as including decisions on non-infringement as well as revocation of the patent. AG Wathelet reached the view that there was no infringement of Article 101(1) TFEU as:

(i) the commercial purpose of the agreement was to enable the licensee to use the technology while averting patent litigation; and

(ii) Genentech was freely able to terminate the agreement by giving reasonable notice, in this case, a "very short" notice period of two months.

AG Wathelet considered that Genentech's "freedom of action was not restricted in any way during the period after termination, and it was not subject to any clause preventing it from challenging the validity or infringement of the patents at issue". Genentech's 'use' of the technology ostensibly underlying the patents was therefore sufficient to trigger the obligation to pay the running royalties, even though, in the event, the European patent had been revoked and the US patents were held not, in fact, to have been infringed by Genentech in the US proceedings.

CJEU decision

The CJEU, like AG Wathelet, considered that the question from the Paris Court of Appeal was unclear and should be restated (as it can have a habit of doing) as referring to non-infringement as well as to revocation of the licensed patents.

The Court applied its previous decision in Ottung (C-320/87). That case had established that a contractual requirement providing for payment of royalties for the exclusive use of a technology even after the underlying patent had expired did not infringe Article 101(1) TFEU as long as the licensee is free to terminate the contract by giving reasonable notice. In the Genentech case, the CJEU extended this principle to cover situations where the validity and infringement of the relevant IPRs was not resolved. The CJEU rejected the argument that the obligation to pay royalties had undermined competition by restricting the freedom of the licensee on the grounds that Genentech was free to terminate the licence by giving reasonable notice so the restriction on its freedom of action was negligible.

The Court also held that the question of whether the royalties were actually payable as a matter of contract law was a question for the proper law of the contract. The Court's ruling related only to the question whether competition law made the underlying contractual provision unenforceable. Once that question had been resolved, the contract was then to be construed and enforced in line with the applicable national law. In this case, according to the referring Court, German law did not preclude an obligation to pay royalties for the period before the agreement was terminated, even though the finished products were held to be non-infringing of the US patents in the US proceedings.

Practical implications

This case extends the Ottung principle, confirming that Article 101(1) TFEU does not preclude licensors from enforcing royalty obligations, even if the underlying IPRs are no longer valid or are revoked, or if the licensed products are non-infringing, provided the licensee can freely terminate the agreement upon reasonable notice.

The position established by this case under EU competition law differs from that in the US. In Kimble v Marvel Entertainment the US Supreme Court refused to overturn the principle it laid down in Brulotte v Thys (derived from patent policy as opposed to antitrust considerations) that a patent holder cannot charge royalties for the use of its invention after its patent term has expired. However, in practice the actual effect of the Brulotte and Kimble v Marvel jurisprudence may not differ that significantly from Genentech. It seems that the US cases are not in fact absolute bars to the receipt of royalties post expiry / revocation / finding of non-infringement. The US Supreme Court in Kimble provided examples of practical solutions to avoid the effect of its decision such as deferring payments for pre-expiration use of a patent into the post-expiration period (e.g. a licensee could agree to pay royalties of 10% of sales during the 20 year patent term but to amortize that amount over 40 years), or by tying post-expiration royalties to a non-patent right such as trade secrets (provided the royalty rate is reduced accordingly).

Post Genentech, it is clear that 'extended' royalty payments that cover a longer period than the period of enforceability of the IPR in question will in principle be compatible with EU competition law. For agreements with a US dimension, licensors should be careful in relying on the receipt of royalties post-expiry, revocation or a finding of non-infringement and may wish to make clear that any such royalties are deferred consideration for pre-expiration use. Parties to global licences should also consider how other jurisdictions interpret such royalty provisions to ensure the obligation to pay remains enforceable. Similarly, how the UK courts will interpret such provisions in the event of Brexit remains to be seen. Licensees across all jurisdictions should consider negotiating specific provisions that terminate royalties in the event of expiry, revocation or a finding of non-infringement of the individual IPR in question to avoid residual liability for unenforceable rights. However, in licences where post-expiration, revocation or a finding of non-infringement royalties are deferred consideration for prior use when the IPR was enforceable, negotiations may be complex as licensors are likely to require this to be taken into account.

Interestingly, on a subsidiary point relating to the role of competition law in arbitration proceedings, Hoechst and Sanofi-Aventis submitted to the CJEU that French law "prevent[s] any review of international arbitral awards as to their substance" and that the courts may only do so in cases of "flagrant infringements of international public policy". AG Wathelet rejected this submission and opined that "limitations on the scope of the review of international arbitral awards … are contrary to the principle of effectiveness of EU law" and parties to a potentially anti-competitive agreement "cannot put these agreements beyond the reach of review under Articles 101 TFEU and 102 TFEU by resorting to arbitration." The CJEU did not consider this particular point in its judgment, but did mention that the Cour de Cassation (France's highest appeal court) dismissed the appeal brought by Hoechst against the decision requesting a preliminary ruling.

57 Genentech v Hoechst and Sanofi-Aventis (C-567/14)

Commercial

Our Commercial practice

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.

The revolutionary gene editing technology: CRISPR-Cas9

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CRISPR (pronounced Crisper), or rather CRISPR-Cas9, is a gene editing technique. Unlike existing gene editing techniques, this ground-breaking technology[58], discovered only in the last five years or so, has given researchers a much-needed simple and efficient tool for genome editing.

Thanks to the CRISPR craze[59], we now potentially have in hand the ability to re-programme any DNA, including our own. Unsurprisingly therefore the power of this technology has led to a plethora of ethical debates and opinions involving research organisations, funding entities and people from all walks of life. Although phrases like 'designer babies' and 'Frankenstein foods' have been reintroduced into our daily parlance, the potential of CRISPR-Cas9 has also created a new wave of hope particularly in relation to generating improved plants and crops, eradicating pathogens, generating biofuel producing micro-organisms and treating diseases.

Research laboratories throughout the world are fast adopting and incorporating this gene editing technique into their research projects and so the likelihood of the outputs of such research projects being exploited on a commercial basis is increasing. Given that the ethical and moral debates around gene editing are in the process of taking centre stage, the obvious question to ask is - do existing law and implementing regulations anticipate and/or address gene editing? The answer is yes, certainly the technologically advanced countries have in place legislation setting out the framework around genetic manipulation of any organism. In this article we provide a whistlestop tour of how the existing EU laws view gene editing, particularly in the UK.

Gene editing in organisms other than humans

While the bulk of the media interest is around gene editing in human cells, there are a large number of research groups carrying out research into modifying DNA in crops and livestock. Disease-resistant crops has always been an appealing concept but the cost of producing genetically modified crops using existing gene editing techniques has been high and commercially unsustainable until now. So far, crops that have been genetically modified and released have either been commodity crops or animal feed. The advent of CRISPR-Cas9 may very well change that. Indeed there have been several recent publications in which CRISPR-Cas9 has been employed for improving properties of crops and plants such as developing sweeter oranges[60] and genetically modifying wheat to improve its resistance to fungal infections[61].

Genetic modification of plants brings with it understandable environmental concerns such as risks of cross pollination that could result in the genetically engineered mutations being transferred through relatives of the genetically modified plants in the wild. The legislation in Europe and particularly in the UK therefore provides a strict legal framework. The EU Directive 2001/18/EC ('GM Deliberate Release Directive') deals with the release of genetically modified organisms (other than humans) - 'GMOs' - into the environment and the placing of GMO's or products containing GMOs within the European community and Regulation No 1829/2003 ('GM Regulation') deals with the placing of food or feed containing GMO on the European market.

Cultivating GMO's

The growth of GMOs is permitted under the GM Deliberate Release Directive but such growth and release is subject to an

intensive authorisation procedure which involves individual risk assessment by the competent authority of the relevant Member State. In the UK, the assessment of the application is the responsibility of the Department of Environment, Food & Rural Affairs ('DEFRA') and is taken by an independent committee - the Advisory Committee on the Release to the Environment ('ACRE'). ACRE reviews each application and advises DEFRA whether to reject or grant consent.

The UK is more stringent in terms of commercial cultivation of GMOs and at present GM crops are not grown commercially in the UK, although their import is permitted. In the UK, the Environmental Protection Act 1990 ('Environment Act'), particularly Part IV of the Environment Act, is the main legislation addressing GMOs and the Genetically Modified (Deliberate Release) Regulations 2002 ('Deliberate Release Regulations') implement the GMO Deliberate Release Directive in the Environment Act. The main aim of Part IV of the Environment Act is to ensure that all appropriate measures are taken to avoid damage to the environment which may arise escape of release of GMO's. In the UK, planting of GM crops for research purposes and therefore deliberate release of a GMO is permitted by making an application in writing to DEFRA.

Up until recently, once authorisation under the GMO Deliberate Release Directive was given in relation to a GMO (e.g. a genetically modified seed or plant propagating material), the Member States were not authorised to prohibit or restrict the free circulation of such GMO in the EU (except under specific conditions).

However, the recent EU Directive 2015/412 allows the Member States more flexibility to decide whether or not they wish to cultivate such genetically modified seeds in their territory. The scope of this legislation clearly demonstrates that there remains a significant amount of concern around the release of plants or other organisms in the environment that have been genetically modified, particularly as the consequences of such release remain unknown and unclear.

Marketing GMOs

Whilst each national government has the authority to approve the release of GMOs for research and development purposes, the authority to approve the marketing of genetically modified food or feed or food produced from or containing ingredients produced from GMOs resides with the Commission[62] under the GM Regulation.

The key objective under the GM Regulation is to ensure that the genetically modified food in question does not have any adverse effect on human health, animal health and the environment, does not mislead the consumer and does not differ from the food it is intended to replace[63]. The stringent and thorough safety assessment procedure is carried out by the European Food Safety Authority ('EFSA')[64] with input from national authorities. The EFSA provides its opinion to the Commission which then informs the applicant of its decision whether or not to permit placing of a GMO food product on the market.

Gene editing in humans

An obvious application of CRISPR in humans would be the correction of diseased genes. Research groups are already testing this procedure on mice[65] with the aim of finessing this technology for human gene therapy.

Somatic and germ cell mutations

When it comes to correcting or changing faulty genes in humans using CRIPSR, a few options spring to mind. One option would be to remove somatic cells (that are non-reproductive cells) from a patient, edit the faulty gene using CRISPR in the lab to correct the harmful mutation and re-introduce the cell with the correct gene back into the patient. Another mechanism would be to target specific human tissue expressing the aberrant gene and introduce into it a correct gene via a carrier such as a virus that is incapable of infection.

A more controversial mechanism would be the correction of the faulty gene at a germline level (i.e.in egg cells, sperm cells and embryos) so that the genetic abnormality that is the cause of the disease is not inherited by future generations.

Legislation addressing gene therapy has been established for some time and continues to develop further as development and clinical testing of gene therapy products is, thanks to technologies like CRISPR, yet again picking up momentum. Under EU law, a medicinal product that incorporates or uses genes or cells is considered to be an advanced therapy medicinal product ('ATMP') and its clinical development and marketing authorisation is subject to Regulation 1394/2007 ('ATMP Regulation') together with the Clinical Trial Directive 2001/83/EC ('Clinical Trial Directive'). Bringing an ATMP to market is a tricky affair both from a technical and regulatory perspective and so there is a raft of additional supporting legislation. For example, where tissues and cells are being used as starting materials, the donation, procurement and testing of the cells are covered by the Tissues and Cells Directive (2004/23/EC) and in the UK, the removal, storage and use of human tissue is subject to the Human Tissue Act 2004.

Other notable supporting legislation includes Directive 2005/28/EC that lays down the requirements for authorisation of the manufacturing or importation of ATMPs.
Whilst clinical trials involving ATMPs and the manufacture of ATMPs fall under the auspices of the competent authority of the Member State, marketing authorisation of the ATMP follows an EU-centralised procedure.

The advent of CRISPR has renewed interest in gene editing at a germline level, with a Chinese academic group recently reporting an attempt to modify the gene responsible for !-thalassaemia, a potentially fatal blood disorder, using CRISPR-Cas9. The legislation for use and manipulation of human embryos is unsurprisingly stringent and at present in the UK there is a prohibition on implanting genetically modified embryos under the Human Embryology and Fertilisation Act ('HEFA'). The Human Fertilisation and Embryology Authority ('Authority'), amongst other roles, regulates the use of embryos in research and has the authority to grant licences in the UK for use of research projects involving embryos. This authority has only recently been exercised

with an academic group based at the CRICK Institute in London applying to and receiving from the Authority a licence to use CRISPR for gene editing in embryos.

Conclusion

Aside from the environmental consequences and the possible disturbances to the ecosystem,concerns remain around the safety of the CRISPR-Cas9 gene editing tool. In the CRISPR-Cas9 system, a genetically engineered component is introduced into the cell which facilitates the mutation of the particular gene of interest. Despite the demonstrated targeted efficiency of this engineered component, there remain concerns that the engineered CRISPR-Cas9 could over time target other genes of the relevant organism genome thereby producing unpredictable and unwanted affects. In addition, concerns remain as to whether the technology is robust enough to ensure that the mutation is corrected in all the relevant cells.

The range of legislation is therefore intended to ensure that a GMO is not released in the environment or a somatic or germline correction of a mutation is not introduced in a human at a tissue or embryo level unless there is enough evidence to demonstrate that the risk of the gene editing tool or the corrected mutation producing unwanted consequences is negligibly low. Despite the technical and ethical challenges, once tweaked, finessed and finalised, CRISPR-Cas9 has the potential to positively affect our environment. From introducing genetically-modified pathogens to potentially eradicating malaria by releasing genetically engineered mosquitoes that do not transmit the malarial parasite, this technology is destined to hold the spotlight for the next few decades.

At present, the legislation certainly in the UK appears adequate to support gene editing at its present stage of development. However there is a recognition that gene editing and associated technologies are rapidly developing and so there may come a time when the law may need to catch up with advancements in the technology. Until then, the world watches the exploitation of CRISPR-Cas9 with great interest.

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Q&A

What is your vision of Carrick?

Carrick does not have the typical biotechnology business model that focuses on a particular technology or mechanism of action. We wanted to create a leading European oncology company which targets multiple mechanism of actions for multiple aggressive tumours. Carrick aims to achieve this by linking together multiple leading investigators and drug development experts from around the world under one roof.

How does Carrick's unique business model distinguish it on a commercial basis from the existing oncology focussed biotechnology and pharmaceutical companies?

In order to deliver cost effective oncology therapies and products that treat a range of cancers, we aim to run a streamlined company with low infrastructure and running costs. We believe our plan to link a network of clinicians and scientists in internationally leading research institutes and hospitals will further contribute to achieving our objective.

Further to this, it is our firm view that it is not just the right compound or the right IP in relation to the compound that provides the commercial advantage, it is having the right people on board that gives us the edge. This is why we are assembling a preeminent team of stakeholders that are experts in their fields be it scientific, commercial, financial or legal expertise.

Do you believe that Brexit will have an impact on the flourishing R&D environment?

From Carrick's perspective, our investors were interested in the opportunity and our location in Europe did not matter.

European organisations and institutions, including those in the UK, are currently at the forefront of producing exciting and ground breaking technologies. The challenge we face is that of investment as European biotechnology companies in general remain undercapitalised when compared to their Northern American counterparts. That being said, I believe that UK innovation in particular is not going unrecognised and that going forward, there will be more investment from the US into Europe.

Dr Elaine Sullivan
CEO
Carrick Therapeutics Ltd

Carrick Therapeutics Ltd, a unique new venture in cancer treatment, recently announced it had secured $95M in funding from some of the most eminent providers of early stage capital. Its Chief Executive Dr Elaine Sullivan, has more than 25 years' experience working in the pharmaceutical industry in the US and the UK. She was formerly Vice President Global External R&D at Eli Lilly and, prior to that, Vice President R&D, New Opportunities at Astrazeneca. Dr. Sullivan is also a non-executive director on the board of IP Group and a member of the Supervisory Board at Evotec AG.

Secondary1st

Bristows LLP is proud to support Secondary1st, a charity founded in honour of our friend and colleague, Rosie Choueka.

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

Currently, all the funds Seondary1st raise are being donated via Breast Cancer Now to the research of Professor Andrew Tutt, who works at the Institute of Cancer Research, as well as a number of other centres.

Professor Tutt's work focuses on triple negative breast cancer, a particularly aggressive form of the disease that 7,500 women in the UK are diagnosed with every year.

The Challenge

When breast cancer does not have any oestrogen or progesterone receptors or the epidermal growth factor receptor HER2, it is called triple negative breast cancer (TNBC). TNBC lacks some of the proteins that hormone positive breast cancers have, and there are no targeted treatments that can stop the cancer from returning.

This aggressive form of the disease has a much lower survival rate than other types of breast cancer, and more than 7,500 women are diagnosed every year in the UK alone. It also disproportionately strikes younger women. This is just one of the many reasons why it is crucial that we increase our understanding of TNBC and learn how to more effectively treat it as quickly as possible.

Aims of Professor Tutt's Work

Professor Andrew Tutt is a world leader in the field of triple negative breast cancer, and as a consultant oncologist, he is driven to ensure that his work meets the needs of the patients he treats.

Several molecular markers have already been discovered that are specifically associated with TNBC and are partly responsible for the aggressive behaviour of the disease. Professor Tutt and his team are now looking for more genetic or molecular markers that can help them better understand the unique characteristics of the disease.

The team ultimately aims to develop treatments that specifically target TNBC and will improve the lives of the many suffering from the disease.

Research Summary

Identifying and validating biological markers

Professor Tutt's team has shown that one of the biological markers they already identified, the molecule PIM1, is a driver of TNBC and a potential drug target in chemotherapy-resistant TNBC. By looking at the molecular pathways within the cancer cells, they plan to characterise how this molecule allows TNBC to resist chemotherapy treatment and how PIM1 drives the disease. The research will generate a better understanding of how to target molecular drivers that are not only responsible for the survival and proliferation of cancer cells, but also those responsible for developing resistance to therapy.

Drug development

Professor Tutt's team have already identified a protein, called KIFC1 (also known as HSET), as a potential drug target in TNBC patients. They now plan to learn more about the importance of KIFC1 by analysing the structural biology of this drug target. Their data will indicate which parts of the target need to be inhibited with drugs to effectively treat TNBC patients in the future.

Immune system recruitment

The immune system is very much involved in breast cancer and is a crucial part of the cancer's survival and progression. A small protein called Interferon-γ, which affects the behaviour of cells, controls many aspects of immune cell recruitment into tumours.

Following treatment with interferon-γ, the gene IL-15RA is switched on in breast cancer cells. Professor Tutt and his team are building molecular tools to further investigate IL-15RA's role in TNBC. They plan to test the effect of IL-15RA on tumour growth and immune cell recruitment by building a model to learn more about the relationship between TNBC and the immune system. Understanding the nature of this relationship is the first step to finding a way to interrupt or control the interaction of the cancer and the immune system to treat the disease.

To learn more about Secondary1st or to donate, please visit their website **www.secondary1st.org.uk**

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

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.

The Bristows' life sciences team is among the largest in Europe comprising 22 partners and 49 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.

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01

02

03

01
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Liz specialises in patent litigation in the life sciences sector. She has over 15 years experience of representing clients in patent matters in the English Courts all the way up to the Supreme Court as well as in the UKIPO. Liz's background in Natural Sciences (Neuroscience) provides her with an excellent understanding of the technical and commercial issues facing companies this field.

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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.

03
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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.

The information contained in this document is intended for general guidance only. If you would like further information on any subject covered by this Bulletin, please email Dr Robert Burrows (robert.burrows@bristows.com), or the Bristows lawyer with whom you normally deal. Alternatively, telephone on +44 (0) 20 7400 8000.

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