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• Patent issues

BIO SPECIAL EDITION

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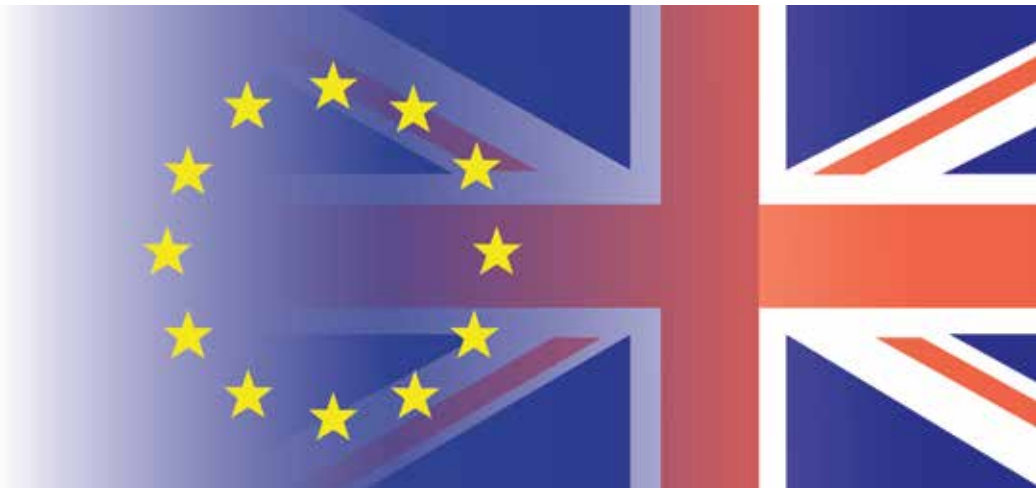
BREXIT DECISION IMMINENT BUT A 'LEAVE' VOTE MEANS IP UNCERTAINTY MAY 'REMAIN' FOR SOME TIME

The UK referendum to leave or remain part of the European Union (EU) will be held on 23 June 2016. A vote to leave the EU will not become effective for a further two years and, in that time, much will have to be decided. In the world of patents, one of the key decisions will be what will happen to the impending Unitary Patent system, which is presently only open to members of the EU, (also true for the current Community Trade Mark and Registered Community Design systems), and the Unitary Patent Court for life science inventions, which is currently being set up in London.

As one of the three countries, along with Germany and France, which must ratify the Unitary Patent for it to come into existence, it is uncertain what the effects may be if the UK leaves the EU. However, it is perhaps likely that the system will continue with the Netherlands replacing the UK as the third mandatory signatory.



Even if the UK does vote to leave the EU, it will still be a part of the European Patent Convention such that patents will be prosecuted through the European Patent Office as normal. After the Unitary Patent system has come into effect, a patent proprietor may obtain a Unitary Patent to protect the invention in most of Europe and the patent will automatically be validated in the UK (provided the patent is in English) and it will then be up to the proprietor to decide if protection in the UK is desired and pay the UK renewal fees.

This may lead to the slightly odd situation that the Unitary Patent Court in London would not have jurisdiction over UK patent rights and litigation of a life sciences patent would have to begin at the UK Courts in London for the UK patent and at the Unitary Patent Court in London for the Unitary Patent effective for other European territories.

In conclusion, leaving the EU may lead to a number of uncertain years for patents as the fine details are worked out. However, it is perhaps more likely that this will all just be a storm in a very British tea cup and nothing at all will change.

IN THIS ISSUE

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HOW MUCH IS ENOUGH TO FALL OUTSIDE THE SCOPE OF A SECOND MEDICAL USE PATENT?

The UK Courts have spent a considerable amount of time over the last few years wrangling over the question of what a generics manufacturer is required to do in order to prevent those they supply with a drug from using it in an infringing way. To put it another way, after the sale of a product or composition indicated for use in a non-infringing way, how much responsibility is on the manufacturer to defend the patent rights of a competitor? This is at the heart of the following cases and, as detailed below, the UK Courts are not averse to requiring that generic drug manufacturers prove they have taken every possible step to ensure that their products are not used to infringe the patents of larger pharmaceutical companies.

WHEN IS A DRUG PRESCRIBED "FOR" PAIN?

- Further developments in the Pregabalin wars

Warner-Lambert v Actavis and Mylan and Warner-Lambert v Sandoz and Lloyds Pharmacy

As a brief reminder of the background of the various recent cases relating to pregabalin, Warner-Lambert had a patent for the drug pregabalin (supplied under the trademark Lyrica) which has now expired. However, they also have a second medical use patent for pregabalin for the treatment of pain which is in force until 15 July 2017. Warner-Lambert alleged infringement by Actavis, a generic manufacturer intending to supply the same drug (under the trademark Lecaent), for off-patent indications including generalised anxiety disorder and epilepsy. The issues of the case surround the extent to which the generic manufacturer can supply the generic drug without care or regard to whether doctors and pharmacists prescribe it for the patented second use.

When a generics company seeks a marketing authorisation for an off-patent drug and there is a patent still in force for a second (or subsequent) medical use, it is normal to identify the off-patent indications in the accompanying summary of product characteristics and the patient information leaflet. The patented indication is said to have been "carved out". This is known as a "skinny label". Activis planned to apply such a label to its Lecaent product. Warner-Lambert argued that this was insufficient to prevent prescription of Lecaent for the patent protected indication of pain relief.

Both Activis and a generic drug manufacturer named Mylan filed for revocation of the Warner-Lambert second medical use patent. These two revocation actions were tried together along with the infringement case. This was a complex case and several issues were referred to the Court of Appeal. However, in September 2015, the High Court issued its full trial decision which found the patent to be partially invalid, and in particular the claims relevant to the issue of infringement (i.e. claims 1 and 3 directed to the use for treating pain and neuropathic pain respectively) were found to be invalid for lack of sufficiency.

Applying the infringement test set out by the Court of Appeal, the High Court judge Mr Justice Arnold also found that, even if claims 1 and 3 had been found to be valid, Actavis has not infringed these claims. The test is based on the interpretation of "for" in the Swiss claim as "suitable and intended for" and consequently requires that the manufacturer (generic manufacturer Actavis) knew or could reasonably foresee that some of his products would intentionally be used for the patented indication. This was found not to be the case and Arnold J granted a declaration that the manufacturer of Lecaent (Actavis), the wholesalers of Lecaent, the doctors prescribing Lecaent, the pharmacists dispensing Lecaent and the

patients taking Lecaent did not infringe the patent.

Following the decision of the High Court, Warner-Lambert applied for an amendment of the claims. The defendants argued that this late amendment was an abuse of process as Warner Lambert had waited until after the decision had been issued to make the application. In a decision of 25 November 2015, Mr Justice Arnold agreed and the application for amendment was stuck out.

However, the parties were given leave to appeal both the above decisions for both validity and infringement and it seems likely that they will do so.

In a further development, it became known to Warner-Lambert that another generics manufacturer Sandoz Limited had created a "full label", i.e. no skinny label, pregabalin drug (supplied as Pragabilin Sandoz) and that Sandoz had shipped over 100,000 packs of this drug to Lloyds Pharmacy Limited. Warner-Lambert made an application to the High Court in order to obtain an interim injunction against both Sandoz and Lloyds Pharmacy.

Mr Justice Arnold held that Sandoz had not attempted to "clear the way" and stated in paragraphs 100 and 101 of the decision:

"It is well established that, where a generic supplier intends to market a product covered by a patent which the generic supplier contends is invalid, then the proper course for the generic supplier is to commence revocation proceedings to "clear the path" for the launch of its product sufficiently far in advance of launch to enable the validity of the patent to be determined prior to the launch date: see SmithKline Beecham v Apotex at [38]-[40] (Aldous LJ). This principle has also been applied in cases where the generic supplier has a non-infringement argument available to it.

In the present case, of course, the validity of the Patent had already been challenged by Mylan and Actavis. Accordingly, there was no need for Sandoz to bring its own action for revocation. The marketing by Sandoz of the Sandoz Full Label Product raises a distinct issue on infringement which did not arise in the Mylan and Actavis proceedings, however. It would have been open to Sandoz to seek a declaration of non-infringement in respect of the Sandoz Full Label Product prior to launch, but it did not do so. To that extent, Sandoz failed to clear the path for its launch of that product."

The outcome of the decision was the issuance of an interim injunction against both Sandoz and Lloyds.

The story of patent rights relating to pregabilin is far from over and we expect to hear more about the appeal in the Warner-Lambert v Actavis and Mylan case later in the year. All of the latest on these cases can be found at www.jenkins.eu.

WOULD YOU LIKE A JELLY BABY WITH YOUR PEMETREXED DIACID?

Actavis v Eli Lilly & Company

Pemetrexed disodium is a chemotherapeutic treatment for lung cancer which has been marketed by Eli Lilly. Alimta is sold as a lyophilised powder with instructions to reconstitute it in a saline solution. Eli Lilly had a European patent for pemetrexed and its pharmaceutically acceptable salts. This patent expired on 10 December 2010. However, protection was extended by a Supplementary Protection Certificate which expired on 10 December 2015. Eli Lilly is also the proprietor of another European patent for the use of pemetrexed disodium in combination with vitamin B12 or a pharmaceutical derivative thereof and optionally a folic protein binding agent. This second Patent will expire on 15 June 2021. Actavis sought a declaration of non-infringement (DNI) from the UK Courts in respect of the French, German, Italian, Spanish, and UK designations of the Patent for their forthcoming Pemetrexed disodium product. Subsequently, as part of the same proceedings, DNI's were also sought for pemetrexed diacid and pemetrexed ditromethamine. In the Court of Appeal decision of 25 June 2015, it was held that Actavis did not directly infringe the Eli Lilly patent. However, if they provided instructions for the product to be reconstituted and diluted in saline

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solution, which was the case at the time, then it was considered that they would be indirectly infringing the patent (contributory infringement).

In this latest case, Actavis applied to the Courts for a declaration of non-infringement for a pemetrexed diacid liquid concentrate product which is supplied with explicit instructions that it must only be diluted in dextrose (glucose) solution. The decision of Mr Justice Arnold on this case was issued on 12 February 2016.

As was written in the decision, Eli Lilly resisted a DNI in respect of the supply of Actavis' products with instructions for reconstitution and/or dilution with dextrose solution on the basis that it was foreseeable that some pharmacists would not follow the instructions contained in the Summary of Product Characteristics (SmPC) to use dextrose solution, but instead would reconstitute and/or dilute the products in saline.

Eli Lilly argued that when stability data became available for the Actavis product, then it was foreseeable that the Acatavis product would be diluted in saline "because of concerns as to the effect of dextrose on patients with diabetes".

Acatavis argued that they had taken every step possible to prevent dilution with saline, including specifically stating this in the SmPC, sending a letter to the relevant competent authorities and medical centres stating this, implementing a policy that Actavis representatives contacting hospitals must explain that the product must only be diluted in dextrose solution, regulating the supply chain including cutting off from further sales any end user found to be diluting the product in saline, implementing a systematic checking of all related worksheets, and making it a contractually binding point in any agreement relating to the product. Indeed, Eli Lilly were not able to suggest any further measures that could be taken by Actavis to ensure that the product is only diluted in dextrose solution.

In addition, Actavis stated to the Court that they would not disclose any stability data for the product in saline and that it had made it part of any contractual arrangement that no hospital or medical centre would be allowed to carry out its own stability study.

Regarding the concern that pharmacists may dilute the Actavis product in saline due to concerns relating to diabetic patients, this was dismissed as unlikely. As one expert witness pointed out to the Court, the amount of dextrose is equivalent to a single jelly baby or 100ml of skimmed milk. Also, it was noted that it was not uncommon to monitor blood sugar levels after administering pemetrexed due to the use of other co-administered sugar compounds.

Mr Justice Arnold held that "it is not foreseeable that the Actavis Product will be diluted in saline. Accordingly, for the foreseeable future, the supply by Actavis of the Actavis product will not infringe the Patent" Therefore, DNI were granted in respect of the UK, French, Italian and Spanish designations of the Patent (a separate decision was issued by the German Courts for the German designation).

PATENTABILITY OF PARTHENOTES IN EUROPE

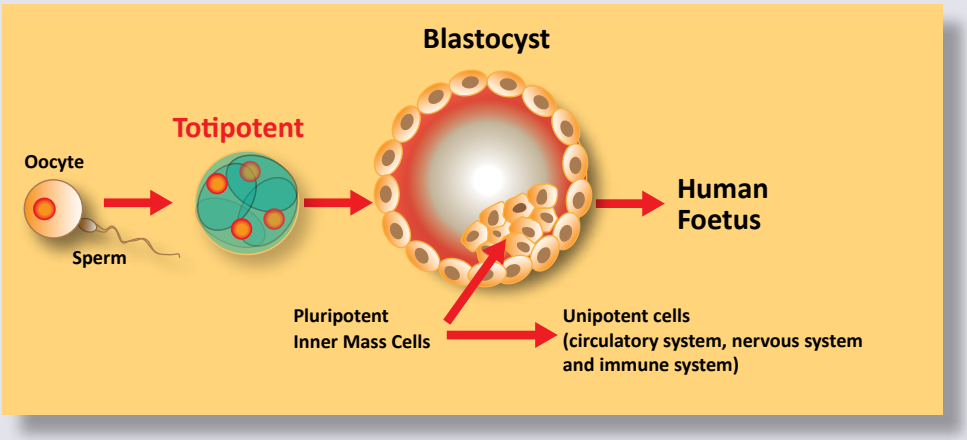
In response to a referral from the UK High Court in the case of *International Stem Cell Corporation (ISCC) v Comptroller General of Patents* (the UK Intellectual Property Office), the Court of Justice of the European Union (CJEU) issued an opinion on the patentability of parthenotes in Europe.

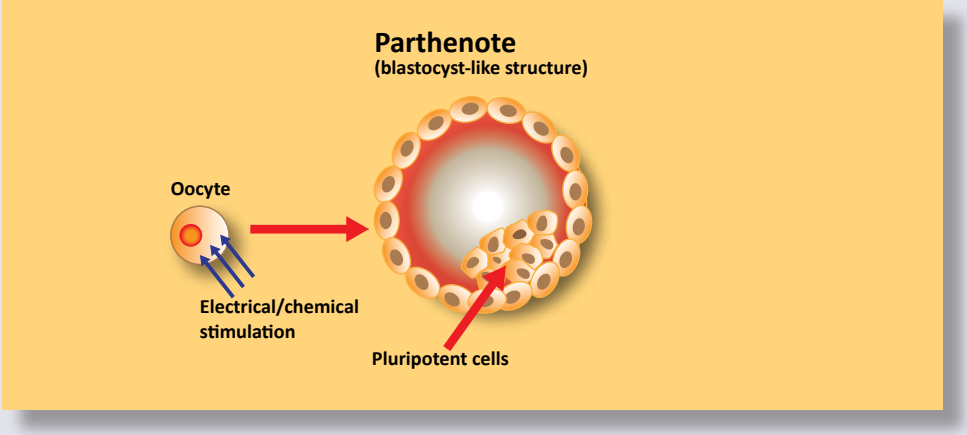
Parthenogenesis is a process that creates a parthenote which has many of the characteristics of an embryo in the early stages of division but, because it was created from an unfertilised ovum, cannot develop further to become a human being. The cells that form the early state of a human embryo are known as 'totipotent' and can go on to differentiate into any cell type, e.g. liver cells, heart cells, etc, whereas, the cells that form the parthenote are 'pluripotent' and cannot differentiate into the full range of cells required to create a foetus.

The referral by the High Court sought to clarify the meaning of the phrase 'capable of commencing the process of development of a human', as the parthenote is incapable of actually developing into a human being. In the prior case of 34/10 (*Oliver Brüstle v Greenpeace*), the CJEU ruled that inventions necessarily involving destruction of an embryo were not patentable, but left several question marks as to what constitutes "an embryo". The CJEU ruled that inventions that necessarily involve the destruction of human embryos were excluded from patentability and stated that the concept of 'human embryo' within the meaning of Article 6(2)(c) of Biotechnology Directive 98/44/EC must be understood in a wide sense. Both fertilised human ova and non-fertilised human ova whose division and further development have been stimulated by parthenogenesis were deemed to qualify as "human embryos" and therefore excluded from patentability.

In their judgement, the CJEU were of the opinion that Article 6(2)(c) of Directive 98/44/EC must be interpreted as meaning that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo'

This judgement provides welcome news to those in the field of stem cell research and provides much needed clarity to what constitutes unpatentable subject matter in Europe after the 34/10 Brüstle case decision.





TODAYS CRYSTAL BALL GAZING MAY BE TOMORROW'S LACK OF SUFFICIENCY -

Regeneron Pharmaceuticals v Kymab Limited and Novo Nordisk A/S

Regeneron were the proprietor to two European patents relating to transgenic mice that could be used as platforms for therapeutic antibody discoveries. The mice in question had a replacement of the mouse variable gene with human variable genes to produce hydrid immunoglobulin.

Regeneron alleged that the defendants infringed these patents. The defendants filed for revocation of the patents.

Mr Justice Carr stated in the decision:

"claim 1 includes the case where the relevant murine sequence is deleted, and also the case where it is moved to a different location and inactivated. Deletion of the relevant mouse gene segments is undoubtedly within the scope of the claim, and repeatedly referred to in the specification."

Upon construing claim 1 it was held:

"claim 1 covers introduction of up to about 300 kb of human sequence. However, there is no upper limit imposed by the claim on the amount of mouse sequence that is to be replaced."

Regarding infringement, the mice strains produced by Kymab were found to fall within the scope of the claims. However, after lengthy expert witness testimony, Mr Justice Carr stated:

"insertions and deletions of this size could not be performed without undue burden in 2001/2, and that the likelihood was that neither of the insertions and deletions referred to in [the specification] would have worked."

It was also noted in the decision:

"the '100 kb out, 200-300 kb in' / '150 kb out, 75 kb in' replacements by homologous recombination are not technically feasible even today, and that they would certainly not have been seen as feasible at the priority date"

Therefore, both patents were found to be invalid and revoked.

This case demonstrates the pitfalls of using unrealistic ranges in order to prevent infringement not only at the time of filing but at any point during the life of the patent. Clearly, the rapid growth of this technology and the prospect that larger sequences would be readily usable with the technology in the future made inserting the claimed sequence lengths highly attractive. However, it is always worth bearing in mind, as frustrating as it may be for the prescient inventor who rightly knows where the technology will be in years to come, a patent application must be sufficiently disclosed at the time of filing.

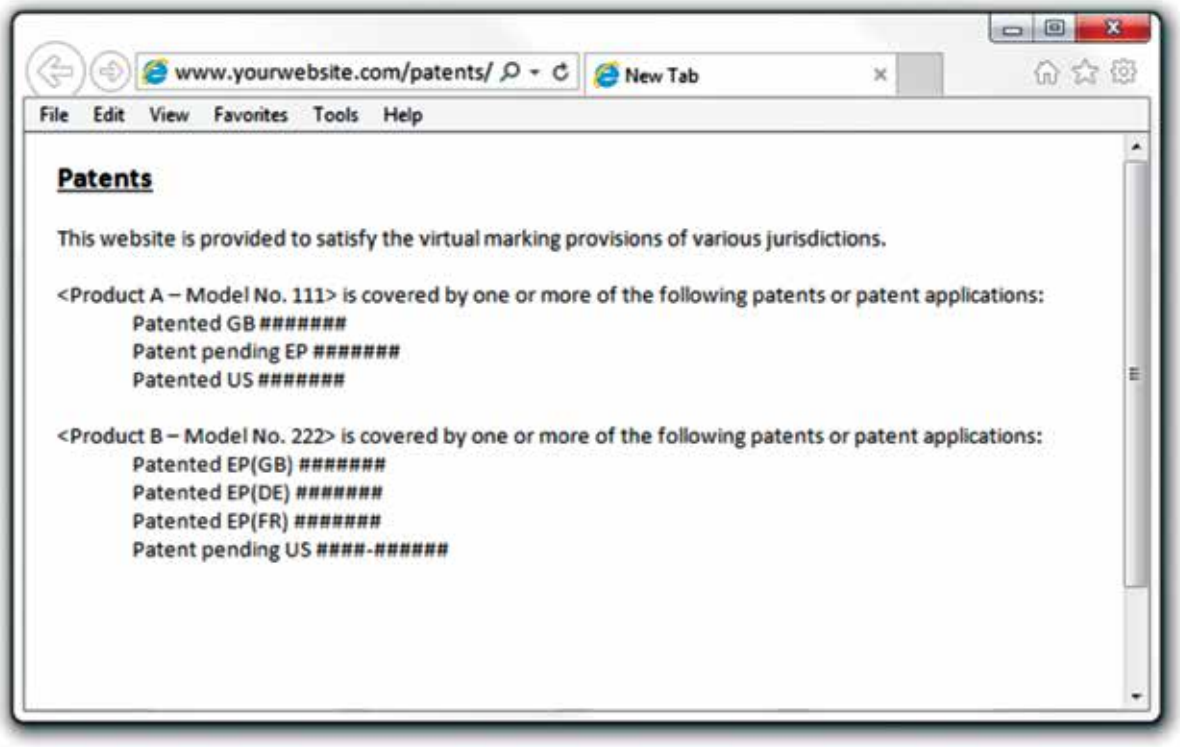
VIRTUAL PATENT MARKING

Recent changes to UK patent law allow "virtual marking" or "webmarking" of products using a web address, pointing potential infringers to a webpage listing details of patents and/or pending applications associated with the products. This practice has been widely adopted in the US since a similar provision of the America Invents Act came into force in March 2013 and is gaining popularity here in the UK.

It is important that patent markings are clear and kept up to date, to ensure that sufficient notice is given to potential infringers of the existence of all relevant patents and pending applications, while avoiding the potentially severe consequences of falsely marking a product as patented. (It is a criminal offence in the UK punishable by fine and whereas we know of no prosecutions to date and the Crown Prosecution Service would not relish such a case, the greater risk would be from a private prosecution brought by an aggrieved competitor.) Webmarking is an efficient and cost-effective way of ensuring all patent markings are kept up to date without the need to mark patent details directly on the product. It also provides a convenient point for the public to access current patent information in relation to a product and thereby negate the defence of "innocence" in any award of damages.

The product or its packaging (or both) should be marked with a web address pointing to the relevant webpage on the company's website.

The webpage should clearly associate each product with the relevant granted patent and/or published application numbers. The products should be clearly identified, for example by including any relevant model numbers and variants that exist. Each time this is updated, a record should be kept (preferably by the patent or legal department) of the change and the date it is posted. As a guide, we provide a sample web page template that is generally suitable for marking patented products in the UK and US:



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Reuben has an honours degree in microbiology and genetics and is a European patent attorney and a UK patent attorney. He has 25 years of experience in advising clients operating in the fields of biotechnology, medtech, medical device patents and chemistry, including representing industrial clients, universities and research organisations; helping SMEs through the creation of strategies for the acquisition, organisation and exploitation of their IP rights. Reuben has a particular interest in fungal genetics/technologies, medical device patents, medtech and laboratory instrumentation such as thermalcyclers and lab-on-a-chip devices.

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Tanya has a degree in Microbiology & Genetics (Hons). Her background is in the biotech field where she has specific experience in dealing with pharmaceutical, medical device and biotech clients. She has extensive experience in working with high-profile blue-chip companies as well as SMEs in relation to their brand management and portfolio reviews. Tanya has over 15 years' experience and provides a commercial approach to her client's trade mark matters.

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Fiona was awarded a PhD in Biochemistry from the University of Cambridge, having conducted research on the structure of the ATP synthase enzyme. Fiona entered the patent profession in 2003 and is an Associate with RGC Jenkins & Co. Fiona is a European Patent Attorney and has passed the UK Patent Attorney qualification exams. Fiona has experience of drafting and prosecuting patent applications, as well as prior art and freedom to operate searching and assessment. Fiona has worked in a wide range of technologies, including biochemical, immunological, chemical and mechanical areas. In particular, she has experience in the areas of medical devices, in vitro diagnostics, biochemical and antibody technologies.

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Edward has a background in microbiology and virology. Following his PhD at Warwick University in the UK, he moved to the United States where he worked as a Research Associate at the University of Virginia studying viral RNA-protein interactions. During his time as a research scientist he presented at a number of international conferences and published several research papers. After returning to the UK, he completed an MSc in Management of Intellectual Property at Queen Mary, University of London. Since joining Jenkins, Edward has had experience in all aspects of patent prosecution and has particular experience in the prosecution of diagnostics, medical device, and microbiological patents.

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