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Critical Review

Case Law: A Review of selected Pharmaceutical Patents in the UK Courts during 2020

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ABSTRACT

Patents lie at the interface between technology and law. This article provides a critical review of four high profile cases from 2020 in which patents relating to pharmaceuticals were litigated in the UK Courts. The selected cases in this review involved 'sufficiency', 'novelty', 'inventiveness', 'plausibility' and 'infringement' issues. The first case is a dispute between Regeneron Pharmaceuticals and Kymab Ltd in relation to Regeneron's patent for a transgenic mouse platform. The second case relates to Pfizer's patent for their Prevnar[®]13 pneumococcal vaccine and the alleged infringement of this patent by Merck Sharp & Dohme. The third case concerns the validity of a patent belonging to Neurim Pharmaceuticals Ltd relating to a slow-release formulation of melatonin for treating primary insomnia. The final case is a dispute between FibroGen Inc. and Akebia Therapeutics concerning FibroGen's patents for hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors ("HIF-PHIs") for use in treating anaemia. The article aims to focus on the technology behind the patents and to provide an insight into how science interacts with law in the context of patent enforcement and infringement.

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INTRODUCTION

Patents sit at a point at which science and technology overlap with the law. While it is a requirement that attorneys, solicitors and judges working in patents all have a strong grasp of the technology in the sectors in which they work, quite often scientific researchers in these sectors are not exposed to patents at all, or their exposure is limited to the early stages of the life of a patent as inventors helping to prepare patent applications and provide input during prosecution of the applications to grant. Researchers will only very rarely, if ever, be involved in patent litigation.

The following is a review of a selection of cases from 2020 in which patents relating to pharmaceuticals were litigated in the UK courts. The authors of this review hope to provide researchers in the

pharmaceutical fields with an insight into how science interacts with the law during patent enforcement.

The authors do not intend the review to provide an in-depth analysis of the legal points in the issues but rather intend to focus on the technology involved and to identify how the basic principles of patentability and infringement were applied in the context of the issues at hand.

REGENERON PHARMACEUTICALS INC V KYMAB LTD [2020] UKSC 27

In the early 2000's, it was widely recognised that antibodies (immunoglobulins) developed using mouse (murine) platforms could be used to treat human disease. Antibodies are made by B cells and contain four polypeptide chains consisting of two

identical “heavy” chains and two identical “light” chains to form the characteristic antibody “Y” structure (Fig. 1).

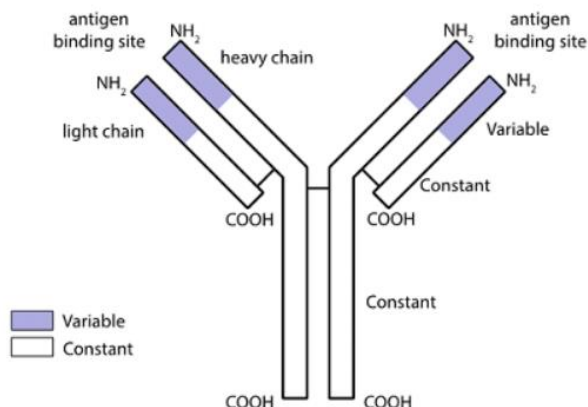


Fig. 1. Top: Schematic of an antibody structure, bottom: Regeneron Pharmaceuticals Inc (respondent) and Kymab Ltd (appellant).

Regions within these chains are known as constant (C), variable (V), diversity (D) and joining (J) as shown in Fig. 2. The heavy chain of an antibody has V, D, J and C segments whilst the light chains have only V, J and C segments. These segments are encoded in the immunoglobulin gene loci and undergo recombination during B cell maturation to produce unique antibodies for targeting specific antigens (Fig. 2).

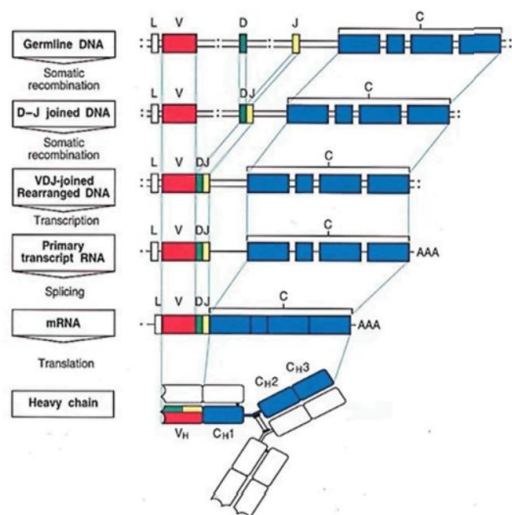


Fig. 2. Schematic of the process or rearrangement, and then transcription and translation of the heavy chain of an antibody.

Antibody therapies which had been approved for therapeutic use at this point (e.g., murine antibodies, chimeric antibodies and humanised antibodies) were known to cause adverse side effects due to the human anti-mouse antibody response (HAMA response).

Fully human antibodies produced in transgenic mice are less likely to be rejected by a patient’s immune system and are more desirable, however said transgenic mice are required to have a suppressed immune response, rendering them immunologically sick and less suitable for antibody development.

The dispute concerned two European patents filed by Regeneron Pharmaceuticals, Inc. in 2002 which described genetically engineered mice having a hybrid gene structure called the “reverse chimeric locus” (Murphy et al., 2002a; Murphy et al., 2002b). This is where mouse variable immunoglobulin gene segments are replaced with human variable immunoglobulin gene segments, whilst maintaining mouse constant region segments. Such mice produce antibodies which differed from other chimeric antibodies known at the time (e.g., antibodies with mouse variable regions and human constant regions). Maintaining the mouse constant regions was found to allow for better compatibility of the antibodies with the mouse immune system and improved the immune response, near to that of wild type mice. In subsequent steps, B cells producing the desired antibodies could be removed and be genetically altered to replace the mouse regions with human regions, thus producing fully human antibodies for use in therapy. The inventive concept is best described in the following claim which was at the heart of the proceedings (Claim 1 from Murphy et al., 2002b):

“A transgenic mouse that produces hybrid antibodies containing human variable regions and mouse constant regions, wherein said mouse comprises an in situ replacement of mouse VDJ regions with human VDJ regions at a murine chromosomal immunoglobulin heavy chain locus and an in situ replacement of mouse VJ regions with human VJ regions at a murine chromosomal immunoglobulin light chain locus.”

The dispute occurred when Regeneron alleged infringement of its patents by Kymab Ltd, who had developed a similar transgenic mouse platform called “Kymouse”. Although infringement was found (UK 2016), Kymab counterclaimed that Regeneron’s patents were invalid for being insufficiently disclosed (Fig. 3).

Sufficiency can be described as a bargain between a patentee and the public, whereby the patentee obtains a monopoly for a new invention in exchange for

disclosing the invention such that it can be worked by the skilled person, thus allowing others to build upon it. Sufficient disclosure is a requirement under both the European Patent Convention and UK law (EPC 2000; UK 1977a).



Fig. 3. Transgenic mouse: Regeneron Pharmaceuticals Inc (respondent) and Kymab Ltd (appellant).

The High Court, and subsequently the Court of Appeal, found that there were significant issues in the methodologies described in the Regeneron patents (UK 2016; UK 2018). In particular, it was found that the key example which described the reverse chimeric locus did not actually work. There were also other concerns, with the patents describing deleting 100 kilobases (kb) of mouse gene sequence and inserting 200-300 kb of human sequence in a single step, and deleting 150 kb of mouse sequence and inserting 75 kb of human sequence also in one step; both unprecedented techniques at the time. Whilst the High Court concluded that Regeneron's patents were not sufficiently disclosed, the Court of Appeal overturned this decision, concluding that the teaching of the patent did at least enable some types of claimed mice to be made, albeit with only a subset of human V gene segments, rather than the full range of human V segments.

By the time the dispute reached the Supreme Court (UK 2020a), technology had developed to the point where mice with the full range of human V gene segments in the hybrid gene structure could be made, which included the most important and commercially valuable mice protected by Regeneron's patents. However, as the test sufficiency is determined at the priority date of the patent (earliest filing date in a family of patent applications for an invention), the Supreme Court disagreed with the Court of Appeal

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and concluded that "the claim to a monopoly over the whole of that range went far beyond the contribution which the product made to the art at the priority date, precisely because mice at the more valuable end of the range could not be made, using the disclosure in the patents". As such, Regeneron's patents were found to be invalid for insufficiency.

MERCK SHARPE & DOHME V WYETH LLC [2020] EWHC 2636 (PAT)

Streptococcus pneumoniae (also referred to as "pneumococcus"), is a gram-positive bacterium having a polysaccharide capsule (Fig. 4). More than 90 serotypes of pneumococcus have been identified, each having a different polysaccharide structure displayed on their surface.

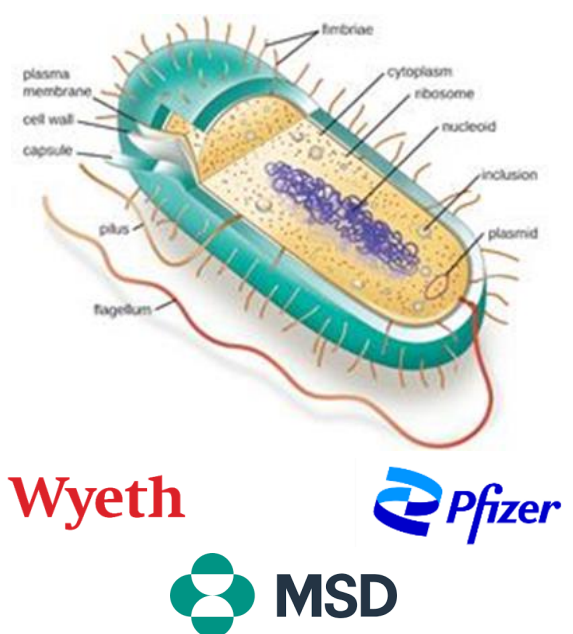


Fig. 4. Top: Schematic of a polysaccharide encapsulated bacterium, bottom: Defendant Wyeth (now Pfizer) and claimant Merck Sharpe & Dohme (MSD).

Pneumococcus resides innocuously in healthy individuals, typically colonizing the respiratory tract, sinuses, and nasal cavity. However, in people having weaker immune systems, such as the elderly and infants, the bacterium can become pathogenic (opportunistic pathogen) and spread to other locations causing diseases such as pneumonia, septicaemia, and meningitis. Pneumonia is the single largest infectious cause of death in children worldwide and accounted for 15% of all deaths of children under five years old in 2017 (WHO, 2021).

Pneumococcal polysaccharide vaccines have been licensed for many years and have proved valuable in preventing pneumococcal disease in elderly adults and high-risk patients. However, these vaccines are not generally effective in infants and children due to a poor immune response to pneumococcal antigens. To address this problem, polysaccharide-protein conjugate vaccines have been developed. In these vaccines, the weak polysaccharide antigen is conjugated to a carrier protein (adjuvant) to elicit a stronger antibody response than is achievable with vaccines based on capsular polysaccharides alone.

Pevnar13[®] is a 13-valent (polyvalent) polysaccharide vaccine against pneumococcus produced by Pfizer (formally Wyeth – the defendant). It comprises purified polysaccharides from 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) each conjugated to a non-toxic diphtheria toxin carrier protein (CRM197). Pevnar 13[®] and its heptavalent predecessor, Pevnar[®] are covered by several patents, including the patent which forms the basis of this High Court decision (Lakshmi et al., 2019).

The dispute began when Merck Sharp & Dohme (MSD) sought to revoke Wyeth's patent (Fig. 4). Wyeth counterclaimed for alleged infringement of their patent by MSD's 15-valent vaccine, V114 which was at the time undergoing clinical trials (UK, 2020b).

The patent at issue is based on Wyeth's discovery that agitation of the vaccine formulation during transport in siliconized containers causes undesirable silicone-induced aggregation of the polysaccharide-protein conjugates. This can result in changes in stability as well as the physical appearance of the formulation, such as colour changes, clouding or haziness, which can cause a patient or consumer to lose confidence in the product. Furthermore, because many immunogenic compositions are often dispensed in multiple-dose containers, uniformity of the dose content of the polysaccharide-protein conjugate over time must be assured. In addition, the immunogenic composition must remain active throughout its "expected" shelf life, wherein break down of the immunogenic composition to an inactive or otherwise undesired form (e.g., an aggregate) lowers the total concentration of the product. Wyeth discovered that aggregation of the polysaccharide-protein conjugates

can be prevented by using a surfactant or an aluminum salt adjuvant in the formulation.

The Court first considered the validity of the patent as challenged by MSD. The main claim of the patent considered by the Court was limited to the use of a formulation to inhibit silicone-induced aggregation of a polysaccharide-protein conjugate comprised in a siliconized container means, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pK_a of about 3.5 to about 7.5, (ii) an aluminum salt, and (iii) one or more polysaccharide-protein conjugates comprising the 13 serotypes found in Pevnar 13[®].

This claim was found to be new or "novel" but was found to lack an inventive step in view of a 2004 paper from Wyeth's workers in Madrid (de la Peña et al., 2004).

Inventive step is one of the criteria that must be fulfilled for a patent to be granted for an invention. An invention involves an inventive step if it is not obvious to the hypothetical "skilled person" or "skilled team" over the state of the art (UK, 1997b). In this case, it was decided that the skilled team would comprise both a vaccinologist and skilled formulator. As vaccine antigens are often proteins, it was considered that the skilled formulator's knowledge would not be limited to vaccines but would also extend to therapeutic proteins.

De la Peña discloses 9-, 11- and 13-serotype conjugated pneumococcal vaccines and says that these vaccines have reached "a very advanced stage of study". On this basis, the Court held that it would have been obvious to the skilled vaccinologist to select the 13-serotype for progression.

It was acknowledged that de la Peña was silent about the claimed formulation features such as the use of an aluminium salt adjuvant, a buffer or a siliconized container, and did not suggest that a siliconized container could cause aggregation problems upon agitation. However, the Court concluded that the patent simply takes forward a very attractive proposal (the 13-serotype vaccine) by routine means, including solving a modest problem (aggregation caused by silicone) in a way which would be within the common general knowledge of the notional skilled team (a surfactant).

Despite finding the patent invalid, the Court went on to consider infringement. Central to the infringement issue was whether the claim was limited to vaccines having *exactly* the 13 serotypes listed in the claim or whether it covered vaccines having additional serotypes. Since MSD's V114 vaccine had polysaccharides for two additional serotypes, there would be no infringement if the claim was interpreted in this way.

The Court took the view that as the serotypes were selected as a balance between efficacy, cross-protection, and ability to be manufactured, the addition of a further serotype would affect the balance, so would not be done arbitrarily. For these reasons, the claim was interpreted narrowly as being limited to a vaccine containing *only* the precise 13 serotypes listed and therefore the Court found no infringement by MSD's 15-valent vaccine.

Since the trial, MSD's V114 vaccine (Vaxneuvance™) has received U.S. FDA approval for its use in adults and has met immunogenicity and safety endpoints in their Phase III trial in healthy infants (MSD, 2021). Pfizer have extended its Prevnar® franchise to include Prevnar 20™, a 20-valent conjugate vaccine which has also been approved for the prevention of pneumonia in adults (Pfizer, 2021).

NEURIM PHARMACEUTICALS (1991) LIMITED & FLYNN PHARMA LIMITED V GENERICS UK LIMITED (T/A MYLAN) & MYLAN HEALTHCARE LIMITED [2020] EWHC 3270 (PAT)

Chronic insomnia affects around 30% of the general population, with increased prevalence in the elderly or those who suffer from psychiatric disorders such as depression. The condition can be classified into two different types: primary insomnia and secondary insomnia. Whilst secondary insomnia is characterised as a symptom of etiologies such as health conditions, medications, pain, and substance abuse etc., primary insomnia is characterised by the absence of such factors i.e., trouble with sleeping is not directly related to an underlying issue.

As explained in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), for primary insomnia "the predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month" and "the

sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning" (APA, 1994). Meanwhile, according to the 10th revision of the International Classification of Mental and Behavioural Diseases (ICD-10), for 'non-organic sleep disorders' it is stated that "insomnia is a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time" (WHO, 1993).

In cases where non-pharmaceutical treatments prove to be ineffective, insomniacs may be prescribed medicaments such as benzodiazepine receptor agonists e.g., triazolam, temazepam and flunitrazepam (Fig. 7). Non-benzodiazepines, which still bind to the benzodiazepine receptor but do not themselves contain the benzodiazepine structure e.g., zopiclone, zolpidem and zaleplon (also known as 'Z drugs', Fig. 7) may also be prescribed. However, there is concern with the use of such drugs, particularly in the elderly but also for the general population, due in part to withdrawal symptoms experienced after long term use. Also, whilst benzodiazepines and similars may reduce the time it takes to fall asleep and increase the duration of sleep, they are not effective for treating certain types of primary insomnia, including primary insomnia characterised by non-restorative sleep.

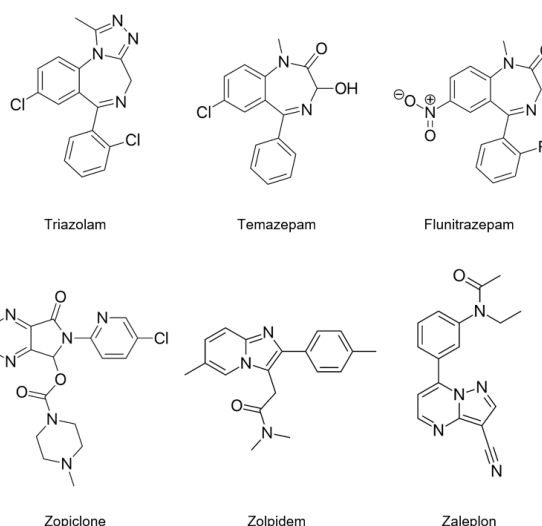


Fig. 7. Structures of benzodiazepine receptor agonists triazolam, temazepam and flunitrazepam (top row), and Z drugs zopiclone, zolpidem and zaleplon (bottom row).

Other medicaments include melatonin (Fig. 8), which is a naturally occurring hormone secreted by the pineal gland and has an important role in the

regulation of circadian rhythms and the sleep-wake cycle. Its production is predominantly influenced by environmental light; during the day, the concentration of melatonin in the blood is very low, increasing in the late evening and peaking at night.



Fig. 8. Top: Structure of melatonin, bottom: Claimants Neurim Pharmaceuticals (1991) Limited and Flynn Pharma Limited and Defendants Generics UK Limited (trading as Mylan) and Mylan UK Healthcare Limited (collectively Mylan).

By the priority date of the patent at the heart of this dispute, there had been many studies looking into the treatment of circadian rhythm disorders and sleep disorders using exogenous melatonin. However, there was at the time little evidence that the administration of exogenous melatonin could be used to treat primary insomnia characterised by non-restorative sleep.

The patent, owned by Neurim Pharmaceuticals (1991) Limited, relates to administering a slow-release formulation of melatonin for treating primary insomnia as defined by DSM-IV and ICD-10 and characterised by non-restorative sleep. The pharmaceutical formulation claimed by the patent is sold under the brand name Circadin, which contains 2 mg of melatonin and is used for short-term treatment of primary insomnia in patients aged 55 years and older (EMC 2021).

Neurim and Flynn Pharma Limited (the exclusive UK licensee) claimed that Generics UK Limited, trading as Mylan, and Mylan UK Healthcare Limited (collectively Mylan) threatened to infringe the patent (Fig. 8). Mylan accepted infringement but claimed

that the invention described in the patent was not novel, lacked inventive step and was insufficient for lack of plausibility (UK 2020c).

The Court found that the patent was novel and inventive over a study published in 1995 by Haimov et al. which discloses administering 2 mg melatonin in a sustained release formulation to elderly insomniacs with melatonin deficiency. The judge took the position that the earlier study differed from the patent as it was focussed on melatonin deficient insomniacs, rather than primary insomniacs characterised by non-restorative sleep as described in ICD-10 or DSM-IV. The patent was also determined to be inventive over Melatonex, a melatonin-containing supplement available in the USA and a review article (Zisapel, 1999) referenced by Mylan, as neither supplement nor review were directed to treating the type of insomniac concerned in the patent. Thus, there was nothing in either disclosure to render the invention obvious to the skilled person.

The patent was also found to be sufficiently disclosed. In particular, the question on sufficiency in this case was that of plausibility i.e., the patent needed to disclose the invention such that the claimed effect of the medicament was at least plausible. In this case, the test of plausibility hinged on the examples within patent, with Example 2 describing a study using 170 elderly primary insomniacs where at least some of whose sleep could be characterised by non-restorative sleep. The study included the use of placebos and was performed as a randomised, double-blind, two parallel group study. A statistically significant improvement in both quality of sleep and daytime alertness for insomniacs taking melatonin compared to the placebo was observed. This alone was enough to convince the judge that the test of plausibility had been met, particularly as the study was focussed on the effect of melatonin on non-restorative sleep in primary insomniacs. Interestingly, although the results of another study (Example 3) were not statistically significant, the judge concluded that the test of plausibility had still been met as the example focussed on the effect of melatonin on non-restorative sleep in 131 primary insomniacs and showed that there was at least “something in” the invention that was beyond mere assertion.

**FIBROGEN, INC. AND ASTELLAS PHARMA
INC. V AKEBIA THERAPEUTICS INC. AND
OTSUKA PHARMACEUTICAL COMPANY LTD
[2020] EWHC 866 (PAT)**

Anaemia is a class of conditions characterized by an inability to produce sufficient quantities of healthy red blood cells to meet the oxygen requirements of the body, and thus is associated with symptoms, including pallor of the skin and mucous membranes, weakness, dizziness, easy fatigability, and drowsiness, leading to a decrease in quality of life. Subjects with severe cases of anaemia show difficulty in breathing and heart abnormalities.

Erythropoietin (EPO) is a naturally occurring hormone which stimulates erythropoiesis, the production of red blood cells (erythrocytes), which carry oxygen throughout the body. EPO is normally produced by the kidneys, and endogenous EPO is increased under conditions of reduced oxygen (hypoxia).

Chronic kidney disease (CKD) describes a diminution in renal function through irreversible damage to the kidneys to an extent that has negative consequences for the patient, including an impairment of EPO production, and hence anaemia. CKD has been recognised as a leading public health problem worldwide – it affects 1 in 10 people globally, of whom 1 in 5 are affected by anaemia (ISN, 2019; Dmitrieva, 2013).

Anaemia of CKD was traditionally treated with oral or intravenous iron. If iron supplementation did not raise haemoglobin to the target range, patients were treated with EPO replacement therapy consisting of either recombinant human EPO (rhEPO) or erythropoietin stimulating agents (ESAs). Despite the clinical success of these therapies, ESAs have been associated with increased risks of cardiovascular events and mortality (Solomon 2010; Koulouridis, 2013). Furthermore, a small number of patients are resistant to ESAs and ESAs have also been known to exacerbate iron deficiency due to ESA-driven supraphysiological erythropoiesis in which the rate-limiting step is the delivery of iron from its stores to erythroblasts (Hayat, 2008, Karlsson, 2011).

Between 2001 and 2004, US biotech FibroGen filed a number of patents relating to the use of hypoxia-

inducible factor prolyl hydroxylase enzyme inhibitors (“HIF-PHIs”) for treating various types of anaemia and related conditions. HIF-PHIs reversibly inhibit prolyl hydroxylase domain (PHD) dioxygenases, which act as cellular oxygen sensors and control the activity of HIF, a transcription factor that regulates renal EPO production and iron metabolism (Haase, 2017).

In September 2019, Astellas (an exclusive licensee in the UK of the six FibroGen patents) obtained a marketing authorisation in Japan for the first oral HIF-PHI product, roxadustat (Fig. 13), and intended to launch the product in the UK (and elsewhere), with the hope that this product will reach blockbuster status by 2023. In 2018, Akebia and Otsuka brought six revocation proceedings against FibroGen to ‘clear the way’ for their HIF-PH inhibitor, vadadustat (Fig. 13) (which is currently in Phase III clinical trials). Consequently, Astellas brought a cross-claim for threatened infringement (UK, 2020d) of FibroGen’s patents.

The High Court first considered the validity of the patents. The patents were split into two families - Family A (Klaus, 2013a; Klaus 2013b; Klaus 2013C) and Family B (Klaus 2013d; Klaus 2013e; Klaus 2013f) - each family derived from a common international (PCT) application. Both families claimed a broad class of heterocyclic carboxamides, with sub-claims to single compounds. The Family A patents related specifically to the treatment of anaemia of CKD, whilst the Family B patents related to the treatment of anaemia of chronic disease (ACD). Whilst the Family B patents were found to lack inventive step over the PCT application from which the Family A patents were derived, the Family A patents were deemed inventive. However, two out of three of the Family A patents and all of the Family B patents were found to be invalid on the ground of insufficiency. The Court concluded that due to the excessive claim breadth, it was implausible that substantially all the compounds satisfying the structural definition of the claims would have the functional features or therapeutic efficacy required by the claims, such that the invention could not be performed across the scope of the claims without undue burden.

The High Court then considered infringement of the claims. The Court found no threat by the Defendant to

infringe the Family B patents which were limited in terms of medical use. Key to the Court's finding that the Family B patents were not infringed was the lack of evidence to suggest that vadadustat had any advantage over present medicines for the claimed medical uses, which meant it would be unlikely that a clinician would change their prescribing practice and prescribe vadadustat off-label for such uses.

There was no dispute that vadadustat would have infringed some of the claims of the Family A patents had they been valid. The Court also considered "infringement by equivalence" of the only valid Family A patent (Klaus 2013b). This type of infringement occurs when an allegedly infringing product falls outside of the literal meaning of a claim but infringes the patent because it is considered to be an equivalent to the claimed invention. This patent was amended during the trial to limit the claims to a specific compound (Compound C) (Fig. 13). Despite the similarities between vadadustat and Compound C, FibroGen was unable to persuade the Court that vadadustat worked in substantially the same way as Compound C, and thus no infringement was found.

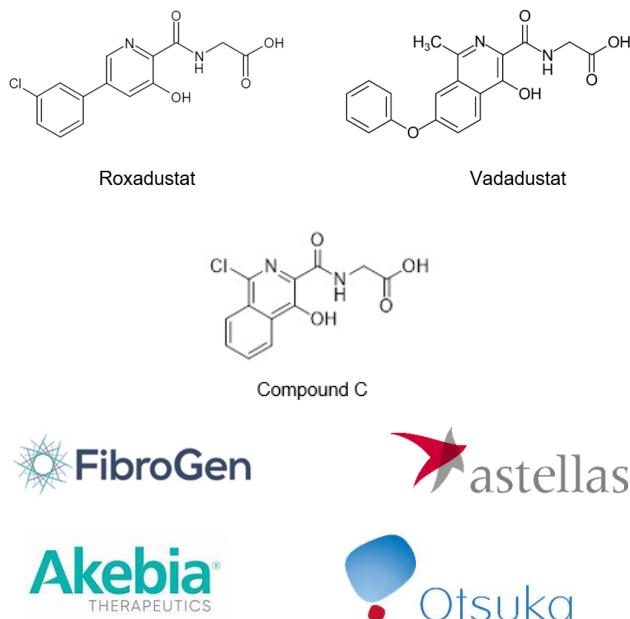


Fig. 13. Top: Roxadustat (EVRENZO™), vadadustat and Compound C, bottom: Claimants FibroGen, Inc. and Astellas Pharma Inc. (exclusive licensee in the UK) and Defendants Akebia Therapeutics Inc. and Otsuka Pharmaceutical Company Ltd.

More recently, the Court of the Appeal handed down its judgment in the combined appeals for this case. Whilst the Court of Appeal agreed that the Family B Patents were invalid for lack of inventive step, in a significant departure from the High Court decision, it

was found that the key claims of the relevant Family A patents were sufficient and therefore valid. This means that Akebia were to launch an anaemia drug containing vadadustat for the treatment of CKD, they would infringe FibroGen's patents.

Shortly before the Court of Appeal judgement, Astellas received European Commission approval for its First-in-Class EVRENZO™ (roxadustat) for adult patients with symptomatic anaemia associated with CKD (Astellas, 2021) (Fig. 13). Roxadustat is the first orally administered HIF-PH inhibitor available in the European Union.

CONFLICT OF INTEREST

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