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Critical Review

Case Law: A Review of Selected Pharmaceutical Patents Litigated in the UK Courts during 2022

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ABSTRACT

Patents lie at the interface between technology and law. This review provides a summary of four high profile cases from 2022 in which patents in the pharmaceutical or medical space were litigated in the UK Courts. The first case concerns Astellas' patent for Betmiga® (mirabegron) for overactive bladder. The second case involves a patent to Bristol-Meyers Squibb for Eliquis® (apixaban) for thromboembolic disorders. The third case concerns Novartis' patent for Exjade® (deferasirox) for use in the treatment of conditions involving excess iron in the blood caused by haemochromatosis, *etc*. In the final case, Novartis defended its patent for Gilenya® (fingolimod) as a disease modifying therapy for relapsing remitting multiple sclerosis. 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.

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 2022 in which patents in the pharmaceutical or medical space 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 issue 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.

TEVA PHARMACEUTICAL INDUSTRIES LIMITED & SANDOZ AG V ASTELLAS PHARMA INC., TEVA UK LIMITED, SANDOZ LIMITED [2022] EWHC 1316 (PAT)

Overactive bladder (OAB) is a chronic medical condition characterized by urinary urgency, often accompanied by urinary frequency and nocturia, with or without urge urinary incontinence, in the absence of urinary tract infection or other obvious pathology (Haylen 2010; Meng 2012). OAB can affect people of any age but prevalence of OAB generally increases with age (BJN 2022).

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The pathophysiology of OAB is poorly understood, but it is typically associated with detrusor overactivity (Peyronnet 2019). The detrusor muscle is smooth muscle found in the wall of the bladder. The detrusor muscle remains relaxed whilst the bladder fills with urine and contracts during urination to empty the bladder. Potential causes of detrusor overactivity include nerve damage as a result of abdominal trauma, weakened pelvic floor, infection, and some neurological diseases such as multiple sclerosis and Parkinson's disease.

Initial management of OAB is typically with lifestyle changes (for example reducing fluid and caffeine intake) and behavioural therapies such as pelvic floor exercises and bladder re-training. If these initial steps are not adequately successful, conventional therapies have included antimuscarinic drugs, a subtype of anticholinergic drugs (Athanasopoulos 2011). These work by blocking muscarinic receptors on smooth muscles fibers in the detrusor muscle, preventing binding of acetylcholine and therefore impeding detrusor contraction. However, antimuscarinics are known to have a number of undesirable side effects, including dry mouth, constipation, urinary retention and cognitive impairment.

Over the last decade, β-3 adrenoreceptor (β3-AR) agonists have emerged as viable alternatives to antimuscarinic drugs. The patent at the heart of this dispute (Toshiyuki 2022) relates to the β3-AR agonist, mirabegron (Fig. 1), marketed by Astellas Pharma AG (Astellas) under the name Betmiga®. Mirabegron works via the sympathetic nerve pathway and stimulates β-3 adrenoreceptors causing relaxation of smooth muscle in the bladder (Bragg 2015).

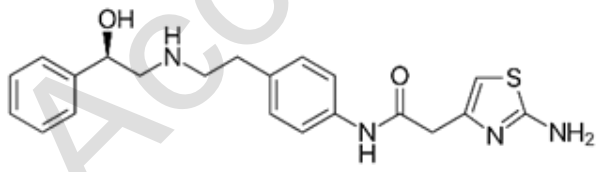

Fig. 1. *Structure of mirabegron (Betmiga®)*

Generics companies Teva Pharmaceuticals Industries (Teva) and Sandoz AG (Sandoz) sought revocation of Astellas' Mirabegron patent. Astellas counterclaimed for infringement which was admitted by both Teva and Sandoz in the event that the patent was found to be valid (UK 2022a).

Fig. 2. *Claimants Teva Pharmaceutical Industries Limited and Sandoz AG and Defendant Astellas Pharma Inc.*

The main claim of the patent was a so-called "second medical use claim" directed to the use of mirabegron as a remedy for overactive bladder. Such claims are used when a previously unknown indication for a known drug is discovered. The core of the revocation action focussed on "obviousness" or inventive step over a piece of prior art cited in the patent, Australian Patent Application AU 199889288 B2 (AU'288).

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 1977).

AU'288 identified mirabegron among other compounds for use in treating conditions such as obesity and hyperglycemia but not OAB (Maruyama 1999). The Claimants' argument was that it was common general knowledge at the priority date of the patent that selective β3-AR agonists had the potential to treat OA and that given the shortage of potent human, selective β3-AR agonists, it would be obvious for the skilled person to test the compounds disclosed in AU'288 as β3-AR agonists in the expectation that they would induce relaxation of the detrusor muscle.

Astellas' key arguments in response were that β3-AR agonism was just one of a number of possible ways under consideration for treating OAB at the priority date and that there was no clinical evidence that β3-AR agonism would even work to treat OAB. Furthermore, Astellas argued that AU'288 did not provide any information about mirabegron's activity and that there may have been many more attractive compounds to choose from.

Whilst the judge accepted that at the priority date the β3-AR agonist mechanism had "momentum" relevant to treatment of OAB, in his view, the Claimants had overstated the skilled person's confidence in relation

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to treating OAB with *any* β3-AR agonist and had oversimplified the situation.

The judge considered that whilst there were review papers at the priority date stating that clinical trials would be needed to assess β3-AR agonists as a potential treatment for OAB, doing those clinical trials would have been in the hope of finding something new and promising rather than a routine matter with an expectation of positive results. Furthermore, the skilled person would have used appropriate caution due to the number of possibilities in play to improve the existing treatments for OAB. Moreover, as a result of the poor quality of the disclosure and limited data relating to mirabegron in AU'288, the judge's position was that the skilled person would understand there to be a substantial degree of uncertainty would not have assumed that any β3-AR agonist would work.

Consequently, the Claimants' obviousness attacked failed, and the patent was found to be valid and would be infringed by the Claimants' proposed acts (UK 2022a).

SANDOZ LIMITED & TEVA PHARMACEUTICALS INDUSTRIES LIMITED V BRISTOL-MYERS SQUIBB HOLDINGS IRELAND UNLIMITED COMPANY [2022] EWHC 822 (PAT)

Clotting processes are crucial mechanisms which prevent excessive bleeding, particularly in instances where damage has occurred to a blood vessel. In the absence of proper blood clotting, experienced by those with disorders such as haemophilia, excessive blood loss can occur in individuals from minor injuries. Conversely, an unwanted blood clot which forms within a blood vessel and obstructs the flow of blood through the circulatory system (known as thrombosis) can lead to complications such as heart attack or stroke.

Anticoagulants (also known, perhaps misleadingly, as "blood-thinning" medicines) are medicines used in the prevention of thrombotic disorders. The most well-known anticoagulants used clinically are warfarin and heparin, both of which have drawbacks. For example, warfarin (first used commercially as rat poison and approved for medical use in the 1950s) has slow onset of action, variability in effectiveness due to food and drug interactions and side effects such as severe bleeding. Heparin, which has been used since the 1930s, must be administered by injection and can also cause severe bleeding, as well as heparin-induced thrombocytopenia (degradation of platelets).

A more recent class of anticoagulant drugs are known as direct factor Xa inhibitors and include rivaroxaban, apixaban, betrixaban, darexaban and edoxaban. Factor X is an enzyme synthesised in the liver which participates in the coagulation cascade *i.e.*, the clotting process. During coagulation, factor X is activated to factor Xa, which in turn activates factor II (prothrombin) to factor IIa (thrombin). Drugs that directly inhibit factor Xa (as opposed to vitamin K antagonists such as warfarin, which have an indirect effect on the coagulation cascade) were identified as promising targets for synthetic anticoagulants in the late 1980s after the discovery of antistasin (isolated from leeches) and Tick Anticoagulant Peptide (TAP) isolated from ticks.

The crystal structure of human factor Xa was published in 1993 (Padmanabhan 1993). Soon after, crystal structures with bound inhibitors were published, showing that small synthetic molecules could bind to factor Xa binding pockets, particularly the S1 pocket (a deep, narrow pocket with hydrophobic walls and an aspartic acid at its base) and S4 pocket (a pocket with a hydrophobic box and a negatively charged cation binding hole). By the early 2000's a number of pharmaceutical companies were reported to have been developing factor Xa inhibitors, with some compounds being found to have Ki or IC5- values in the nanomolar, and even sub-nanomolar range.

The drug apixaban (Fig. 3) is sold by Bristol-Myers Squibb (BMS) under the name Eliquis® for thromboembolic disorders (when a clot has broken free from the point of origin and lodged elsewhere in the body) following a hip or knee replacement operation. Worldwide revenue for Eliquis® in 2022 was $11.8 billion (BMS 2022).

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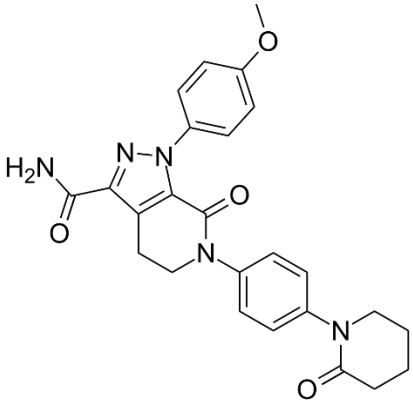

Fig. 3. *Structure of apixaban (Eliquis®).*

Apixaban was claimed in a patent (Pinto 2002) and also a corresponding supplementary protection certificate (SPC) owned by BMS, for which Sandoz and Teva sought revocation (UK 2022b). BMS counterclaimed that both Sandoz and Teva were infringing the patent, which both parties admitted. Thus, the trial concerned the potential revocation of BMS's patent (and SPC), with the proceedings based on a lack of plausibility and a lack of inventive step.

The first issue came down to whether the application, which exemplifies synthesis of over 100 different compounds, made it plausible that apixaban would be an effective factor Xa inhibitor. BMS provided many different lines of argumentation to show that the skilled person reading the patent application would see that apixaban was a preferred compound. However, the judge concluded that the application did not make it plausible that apixaban would have any useful degree of factor Xa binding because there was no reference to apixaban to show that it was a compound for which useful results had been achieved. Therefore, the patent was found to be invalid for lack of plausibility. As a result of this finding, the judge also found that the patent was obvious over an earlier BMS patent (Fevig 1999), which also disclosed apixaban, for lack of technical contribution. The patent was thus found invalid.

Recently, the Court of Appeal rejected an appeal by Bristol-Myers Squibb on the decision invalidating of the patent (UK 2023).

TEVA PHARMACEUTICAL INDUSTRIES LIMITED & TEVA UK LIMITED V NOVARTIS AG & NOVARTIS PHARMACEUTICALS UK LIMITED [2022] EWHC 2847 (PAT)

Iron is an essential element used in the human body for various physiological processes. It is stored within the body by a protein called ferritin and is utilised by other proteins such as haemoglobin, myoglobin, and cytochrome.

Excess iron in blood, known as iron overload, can cause damage to the liver, heart, pancreas, endocrine glands, and joints. Iron overload can be caused by certain blood conditions *e.g.*, haemochromatosis or by receiving blood transfusions. Particularly with red blood cell transfusions, iron from haemoglobin builds up because the body does not have a physiological mechanism to excrete excess iron.

Chelation therapies have been used since the 1960s for treating iron overload. These therapies work by introducing a compound into the body which binds to excess iron, the resulting complex then being excreted. Deferoxamine (Fig. 4), used since the 1960s, requires administration over the course of 8 to 12 hours using a slow infusion pump up to 4 or 5 times a week. This treatment usually suffers from poor patient compliance and severe side effects. Deferiprone (Fig. 4), used since the 1980s, is an oral dosage form which needs to be taken 2 to 3 times a day, but also causes adverse side effects.

A more recent therapy uses a drug called deferasirox (Fig. 4), marketed as Exjade® by Novartis (EMA 2023). The drug only needs to be administered once a day, vastly improving patient compliance. However, the solubility of deferasirox is very poor (0.02 mg/ml in water at 37 °C). Administration requires taking the drug at high dose as a dispersion in liquid and causes side effects including nausea, vomiting, diarrhoea and abdominal pain.

A new swallowable film-coated tablet formulation of deferasirox which mitigated these issues had been developed by Novartis and was the subject of two European patents (Gosh 2014; Gosh 2017). Teva bought revocation proceedings against both patents before the European Patent Office and also before the High Court (UK 2022c). Teva also sought a declaration from the High Court that their own formulation of deferasirox, termed Teva DFX, did not infringe Novartis' patents.

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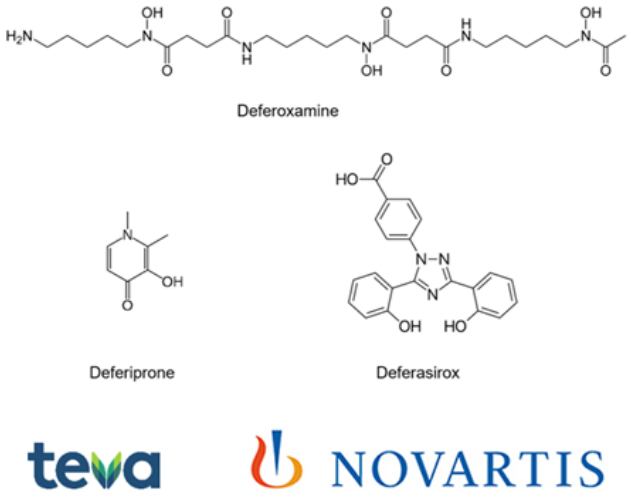

Fig. 4. *Top: Structures of Deferoxamine, Deferiprone and Deferasirox (Exjade®). Bottom: Claimants Teva Pharmaceutical Industries Limited & Teva UK Limited and Defendants Novartis AG & Novartis Pharmaceuticals UK Limited.*

The formulation claimed in Novartis' patents is a swallowable film-coated tablet comprising 45 to 60% by weight deferasirox with six pharmaceutical excipients: microcrystalline cellulose, crospovidone, povidone, poloxamer 188, colloidal silicon dioxide and magnesium stearate. The claims also specified that the tablets did not contain sodium lauryl sulfate and lactose. The patents describe how the new Exjade® formulations achieve more predictable dose-exposure relationships in clinical practice, an absence of a substantial food effect which avoids the requirement to take the drug on an empty stomach at least 30 minutes before food, a more palatable alternative to the currently approved dispersion and improved gastrointestinal tolerability attributed to the formulation being without sodium lauryl sulfate and lactose.

The Judge was tasked with determining whether this claimed formulation had an inventive step over two previous disclosures, referred to as "Battung" and "Zadok" (Batung 2007; Zadok 2009).

Battung discloses an example of a dispersible tablet comprising 42 to 65 % deferasirox, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, lactose and sodium lauryl sulfate. Zadok discloses examples of similar formulations, but also discloses the possibility that such formulations could also be in the form of swallowable tablets. The Judge concluded that the differences between Novartis' claimed formulation and the formulations disclosed in Battung and Zadok was that Novartis' formulation is the use of a different surfactant (poloxamer 188 instead of sodium lauryl sulfate) and a different filler (microcrystalline cellulose instead of lactose). The difference between Novartis' oral tablet formulation and Battung's dispersion was an obvious modification because of known advantages of tablets over dispersion formulations. The Judge also found that the skilled team would be minded to use a different excipients in place of lactose and sodium lauryl sulfate, as certain patients are intolerant to lactose and sodium lauryl sulfate is a gastric irritant. The formulation claimed by Novartis therefore was found to lack inventive step over Battung and Zadok.

The issue of infringement was also addressed and turned solely on the content of deferasirox in Teva DFX, the amount of which is confidential but falls outside the claimed 45 to 60% by weight. On this basis, the Judge also concluded that Teva DFX did not infringe Novartis' patents.

TEVA UK LIMITED & TEVA PHARMACEUTICAL INDUSTRIES LIMITED V NOVARTIS AG [2022] EWHC 2779 (Ch)

Multiple sclerosis (MS) is a neurogenerative disease of the central nervous system that results from immune-mediated damage to the protective myelin sheaths around the nerve cells in the spinal cord and brain. In 2022, it was estimated that there were over 130,000 people in the UK with MS, and that nearly 7,000 people were newly diagnosed each year (MSS 2022).

Relapsing remitting multiple sclerosis (RRMS) is the most common type of multiple sclerosis accounting for about 85% of cases (MSS 2016a). RRMS is characterised by episodes of new or worsening neurologic symptoms with periods of remission in between where symptoms ease. Some symptoms may go away completely, but some may only partially improve or remain unchanged.

RRMS is typically treated with disease modifying therapies (DMTs). DMTs are not a cure for RRMS but can reduce the number and severity of relapses.

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DMTs interact with the immune system to reduce and modulate lymphocyte number, proliferation and trafficking, or cytokine production, thereby reducing neuroinflammation and preventing the occurrence of relapses and new inflammatory lesions (MST 2022).

This case concerns Novartis' DMT, fingolimod (Fig. 5), which was launched in the UK in 2011 as Gilenya® (MSS 2016b). Fingolimod is an orally-administered sphingosine-1-phosphate (S1P) receptor modulator. S1P receptors are highly expressed on membranes of lymphocytes and are critical for T and B cell egress from secondary lymphoid organs (Mazzola 2015). The active metabolite, fingolimod-phosphate binds with high affinity to four of the five S1P receptors subtypes located on lymphocytes causing internalization and degradation of S1P receptors. This results in retention of lymphocytes in the lymph nodes and reduces lymphocyte infiltration into the central nervous system (Chun 2010; Pournajaf 2022).

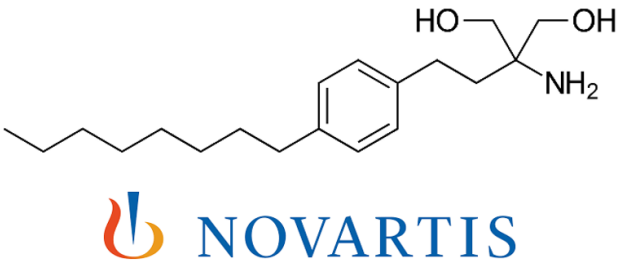

Fig. 5. *Top: Structure of fingolimod (Gilenya®). Bottom: Defendant: Novartis AG.*

Novartis owned an extensive patent portfolio protecting various dosage regimes and formulations relating to fingolimod. The patent at issue EP2959894 (EP'894) claimed a daily oral dosage of 0.5 mg for the treatment of RRMS (Hiestand 2022). Regulatory and market exclusivity for Gilenya® expired on 22 March 2022.

Having already obtained market authorisation for its generic version of fingolimod, in February 2022, Teva brought proceedings against Novartis seeking a so-called *Arrow* declaration (UK 2022d). An *Arrow* declaration is a declaration that a particular product, process or use would have been lacking in novelty, or obvious at the priority date of the patent application, so that the product, process or use cannot infringe any later granted patent (UK 2007). If granted, the *Arrow* declaration would provide a defence in any later infringement action.

In response, Novartis brought infringement proceeding against Teva and a number of other generic companies and sought an interim injunction to prevent launch of the generic versions of fingolimod (UK 2022e). An interim injunction is a temporary injunction sought during legal proceedings before a trial. Novartis' application for interim injunctive relief was refused although there was a short period where the interim injunction was in force whilst Novartis unsuccessfully appealed the decision.

Before this trial, Novartis de-designated the UK from EP'894 meaning that it did not proceed to grant in the UK and therefore the UK is now a generic market for fingolimod. Subsequently, Novartis was able to settle with the other generic companies, but Teva maintained its application for an *Arrow* declaration on the basis that it would continue to serve a useful purpose.

As Novartis did not present any evidence in relation to the question of obviousness, the trial was conducted on the assumption that Teva was correct that the relevant subject-matter was obvious. Therefore, the sole issue for this trial was whether, as a matter of discretion, an *Arrow* declaration should be granted, even though Novartis did not have patent protection for a daily oral dosage of 0.5 mg regime in the UK. After consideration of expert evidence from both sides, unfortunately for Teva, the court concluded that *Arrow* declaratory relief should not be granted. The decision was upheld on appeal (UK 2022f).

CONFLICT OF INTEREST

Harry M. O'Brien is a part-qualified patent attorney, Sarah-Jane Crawford an associate and James A. Stones a partner at Beck Greener LLP, a London based firm of Chartered and European Patent and Trademark attorneys. This article does not constitute legal advice on any specific issues. For any specific matters, a

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personalised advice should always be sought from a licensed attorney.

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