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Critical Review

Case Law: A Review of Selected Pharmaceutical Patents in the UK Courts during 2021

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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 2021 in which patents in the pharmaceutical or medical space were litigated in the UK Courts. The first case is a dispute between Teva and Bayer in relation to a patent for a formulation of Teva's cancer drug, sorafenib tosylate. The second case relates to Alcon's patent for their glaucoma drug, Travoprost and the alleged infringement of this patent by a number of generics companies. The third case concerns the validity of several patents belonging to Illumina relating to labelled modified nucleotides and their use in DNA sequencing methods. The final case relates to a patent for Insulet's OmniPod® device, the first tubeless insulin pump. 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 2021 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 & TEVA UK LIMITED V BAYER HEALTHCARE LLC [2021] EWHC 2690 (PAT)

During pharmaceutical development, an active pharmaceutical ingredient (API) will undergo numerous preformulation tests to establish physical properties including solubility, permeability, chemical stability, pKa, hygroscopicity, melting point and assessment of whether the compound is

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crystalline. Using these results, a formulation scientist will then determine an effective, safe and stable formulation of the API for administration.

Many APIs entering pharmaceutical development have good permeability (*i.e.* ability to move through the semipermeable membranes of the gastrointestinal tract to the systemic circulation) but low solubility. Solubility is a key parameter of interest, especially as APIs must exhibit at least limited aqueous solubility for absorption in the body and therefore therapeutic efficacy. For oral dosage forms, solubility must be considered over the pH range typically encountered in the gastrointestinal tract.

A common way to improve aqueous solubility is by forming a suitable salt of the API. The process of making salt forms of an API and investigating the properties of the salts is called a salt screen.

Sorafenib tosylate, sold under the trade name NEXAVAR®, is an orally administered drug approved in the EU and US for the treatment of various types of cancer (Fig. 1) (EC 2022; FDA 2022). Although the Supplementary Protection Certificates (SPCs) covering sorafenib recently expired, Bayer HealthCare LLC owned a patent relating to a formulation of the tosylate salt of sorafenib (Carter 2012), against which Teva brought revocation proceedings across Europe.

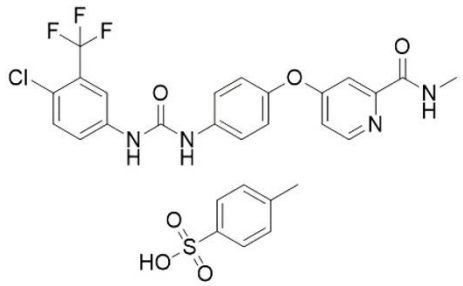

Fig. 1. *Top: Structure of sorafenib tosylate. Bottom: Claimants Teva Pharmaceutical Industries Limited and Teva UK Limited and Defendant Bayer Healthcare LLC.*

Bayer's patent relates to the combination of sorafenib tosylate with 5-fluorouracil. The combination is said to yield better efficacy in reducing the growth of a tumour as compared to administration of either agent alone and provides a higher response rate among treated patients. Indeed, experiments conducted on female mice implanted with human tumour fragments showed the combination to be effective for tumour growth suppression, but interestingly sorafenib tosylate was also shown to have at least a degree of efficacy when used alone. Thus, whilst the majority of the claims in the patent were directed to the combination, the last claim in the patent specified the tosylate salt of sorafenib only. It was this claim which was at the heart of the dispute (UK 2021a), which Teva alleged lacked inventive step over a clinical trial disclosed in a journal article about sorafenib and its utility in cancer therapy referred to as 'Lyons' (Lyons 2001).

Inventive step or "obviousness" 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).

The first question came down to what a skilled team would do when faced with the disclosure of Lyons. Whilst Lyons describes encouraging results in cancer treatment using an oral formulation of sorafenib, the identity of the formulation is not disclosed, giving no direction to use either the free base or any salt form of sorafenib. However, the judge concluded that the clinical trial would be seen as reassuring to the skilled person that a sufficiently soluble formulation of sorafenib for use in an oral administration was possible. The critical question for the judge therefore became whether the skilled person, who would now be motivated to perform a salt screen of sorafenib, would include tosylate in the screen (see Fig. 2), thus arriving at sorafenib tosylate.

Following detailed discussions from Teva and Bayer's expert witnesses, the judge determined that the primary factor in the salt selection process would be the consideration of the pKa range of sorafenib and the pKas of the various counterions; this would have identified tosylate as an attractive candidate. Indeed, it appeared that there was no sufficient reason *not* to try tosylate.

The judge concluded that:

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"*If one compared a number of real skilled teams side by side, having read Lyons and faced with sorafenib, they would select different ranges of salts to test in a first or second tier, albeit with considerable overlap. Some teams who found unpromising results in the first and second tier screen would continue past a second tier screen, others might not. I bear in mind that some real teams might never have selected the tosylate salt for inclusion (depending on their particular experience), but I am satisfied that most would. Above all, the inclusion of the tosylate salt would have been the result of standard and routine considerations.*"

The claim to the tosylate salt of sorafenib in Bayer's patent was therefore found invalid for obviousness.

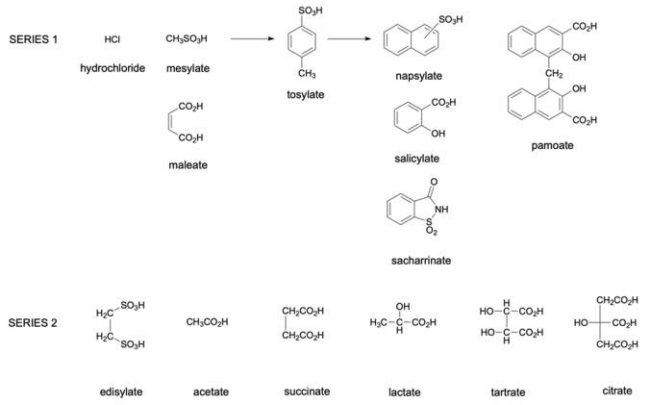

Fig. 2. *A schematic showing sorafenib salt screening, redrawn from Gould (Gould 1986), which was discussed in trial in relation to the common general knowledge of the skilled person.*

ALCON RESEARCH LLC, ALCON PHARMACEUTICALS LIMITED V ACTAVIS GROUP PTC EHF, ACCORD-UK LIMITED, PHARMATHEN SA, ASPIRE PHARMA LIMITED [2021] EWHC 1026 (PAT)

Glaucoma refers to a group of ocular diseases characterised by progressive damage to the optic nerve and associated progressive visual loss. It is the most common cause of irreversible blindness – based on prevalence studies, in 2020 it was estimated that 79.6 million individuals suffered from glaucoma, and this number is predicted to increase to 111.8 million individuals in 2040 (WGA 2022).

Primary open angle glaucoma (POAG) is the most common form of glaucoma in the UK (GUK 2022; Winkler 2014). The most significant risk factor for POAG is elevated intraocular pressure (IOP) (NLM 2022a) which typically arises due to an imbalance in the production and drainage of fluid in the eye (aqueous humor). Over time, the high pressure damages the optic nerve leading to sight loss (NLM 2022b).

Glaucoma is typically treated using topical medications to lower a patient's IOP to prevent further damage to the optic nerve, either by increasing the drainage of aqueous humour or by reducing its production (Weinreb 2014; NLM 2022c).

Naturally-occurring prostaglandins (PGs) have long been known to lower IOP after topical ocular instillation (Camras 1977), but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema (Bito 1997).

In 1994, Alcon filed a patent relating to the use of the drug travoprost (fluprostenol isopropyl ester ("FIE"), a prostaglandin F2α analogue, Fig. 3) for the treatment of glaucoma and ocular hypotension (Bishop 2008). Alcon had discovered that these prostaglandin F2α analogues showed significantly greater IOP reduction than known prostaglandin analogues while having similar or lower side effect profiles. In particular, it was found that the presence of a chlorine atom or a trifluoromethyl group in the *meta* position on the phenoxy ring at the end of the omega chain provided a compound having excellent IOP reduction without the significant side effects found with other, closely related compounds.

Alcon originally sued Aspire Pharma Ltd and manufacturer Pharmathen SA in 2014, for threatened infringement of its patent. In 2015, Alcon also sued British generics company Actavis UK Ltd., subsequently rebranded as Accord-UK Limited, and the two actions were consolidated before trial. The defendants admitted infringement but counterclaimed that the patent was invalid (UK 2021b).

Although the patent had already expired by the time of the trial, the trial was necessary to determine whether cross-undertakings in damages given by Alcon when it obtained interim injunctions would take effect. A cross-undertaking in damages is legally binding promise to the court to compensate the respondent to an injunction for any loss or damage

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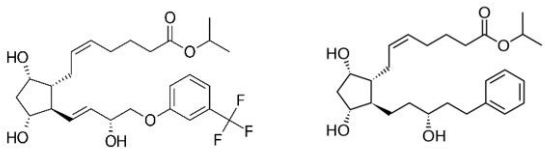
they might suffer if the interim injunction is granted, but later found to be improper.



Alcon

Actavis ASPIRE PHARMA

accord Pharmathen

Fig. 3. *Top: Structure of Travoprost (fluprostenol isopropyl ester (FIE)) and Latanoprost. Middle: Claimants Alcon Research LLC and Alcon Pharmaceuticals Limited. Bottom: Defendants Actavis Group PTC EFH, Accord-UK Limited, Pharmathen SA and Aspire Pharm Limited.*

Validity was attacked on the grounds of lack of novelty over a prior art patent application referred to as "EP'800" (Desantis 1993), and obviousness in view of a paper published by Stjernschantz *et al* (Stjernschantz 1992) which described phenyl substituted prostaglandin analogues for the treatment of glaucoma.

The only reference to an FIE in EP'800 was in a specific example where it was used in combination with another, E series prostaglandin. The main claim of the patent considered by the Court expressly disclaimed the specific combination of travoprost with an E series prostaglandin and therefore the novelty attack failed.

The core of the appeal focused on inventive step. The Stjernschantz paper did not disclose travoprost, but the structurally different prostaglandin F2α anologue latanoprost was identified as a particularly promising compound with positive activity data and reduced side effects in a number of *in vivo* animal models (Fig. 3). The paper also disclosed that latanoprost was undergoing Phase III clinical trials and suggested a hypothesis as to why certain chemical substituents may result in increased activity and reduced side effects.

The question considered by the court was whether it would be obvious to try travoprost for treating glaucoma because it was known to be a potent and selective prostaglandin F (FP) receptor agonist and Stjernschantz showed that it was most probably FP receptor binding that was responsible for reduced IOP.

The judge did not find the defendants' expert evidence to be persuasive, in particular because it failed to deal with why the skilled team would think of travoprost in the first place, lacked analysis of the prospects of success, and did not take account the core teachings the Stjernschantz paper.

The judge considered it important to bear in mind that the overall teaching of Stjernschantz concerned the structure-activity relationships for various synthetic prostaglandin analogues, and specifically the effect of different phenyl ring substituents and omega chain lengths on IOP reduction and side-effects in various animal models. The judge's position was that there were more attractive options that were consistent with the overall teaching and direction of Stjernschantz and therefore that the skilled person would consider further prostaglandin analogues reasoned out of the structure-activity work, rather than selecting structurally different travoprost (which was not even disclosed in Stjernschantz) simply based on its known activity as an FP agonist. The judge therefore rejected the defendants' obviousness attack and declared the patent valid and infringed. As a result, the cross-undertakings given by Alcon when it obtained interim injunctions did not take effect.

ILLUMINA CAMBRIDGE LIMITED V LATVIA MGI TECH SIA ET AL [2021] EWHC 57 (PAT) AND [2021] EWCA CIV 1924

Sanger sequencing is technique used to determine the order of nucleotides in DNA. The method, developed in the 1970's, was so successful that Frederick Sanger was awarded a share in the Nobel Prize in Chemistry in 1980 and automated machines running Sanger sequencing were used in the Human Genome Project in the 1990's.

Sanger sequencing works by synthesising DNA in four parallel sequencing reactions (Sanger 1977). Each reaction mixture has a single-stranded template to be sequenced, a primer, the four standard

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deoxynucleotides (dATP, dGTP, dCTP, and dTTP) and DNA polymerase. The trick to Sanger sequencing is the addition of chain-terminating dideoxynucleotide triphosphates (ddNTPs), whereby one of ddATP, ddGTP, ddCTP, and ddTTP is added to one of the four reaction mixtures at a lower concentration than the standard deoxynucleotides. General structures of dNTPs and ddNTPs are shown in Fig. 4.

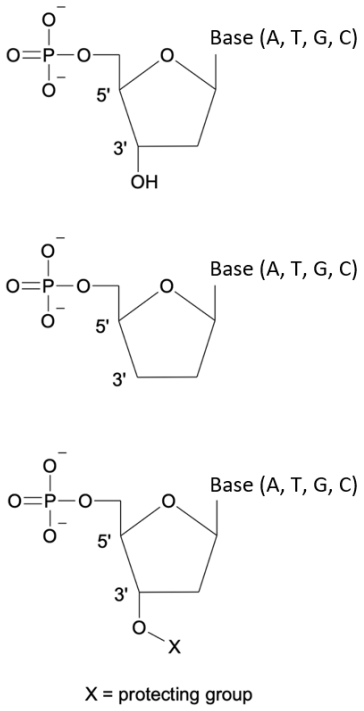

Fig. 4. *dNTPs (top), ddNTPs (middle) and reversable chain terminating protected dNTPs (bottom).*

During synthesis, DNA polymerase adds complimentary bases to the template strand, but upon incorporation of the added ddNTPs, synthesis is terminated. This is because ddNTPs lack the 3′-OH group required to form the phosphodiester bond between one nucleotide and the next, resulting in a number of DNA fragments of varying length. Using gel or capillary tube electrophoresis, the different sized DNA fragments can be resolved and the DNA sequence determined (Fig. 5).

A variant of Sanger sequencing developed later uses a chain terminator that is reversible *i.e.*, nucleotides that, rather than lack a 3′-OH group, instead have a 3′-OH protected group (see Fig. 4). When the reversible chain terminator is incorporated into the DNA polymer, ceasing the incorporation of the next nucleotide, the nucleotide is read by use of an attached radioactive label. The 3′-OH protecting group and label are subsequently removed and the sequencing cycle repeated by the incorporation of the next blocked, labelled nucleotide. This method is known as sequencing by synthesis.

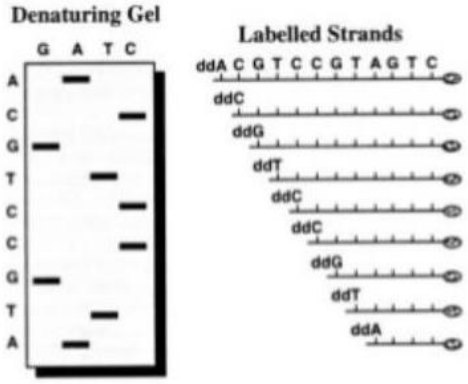

Fig. 5. *Four parallel sequencing reactions resulting in DNA fragments terminated with radiolabelled ddNTPs. Resolution of the different sized DNA fragments allows determination of the strand sequence.*

The difficulty with this process is selection of an appropriate 3′-OH protecting group, which must be tolerated by polymerase enzyme whilst simultaneously be easily removable under mild conditions to not cause damage to the polynucleotide structure. This challenging obstacle can be overcome by the use of an azidomethyl protecting group (Fig. 6). The technology was disclosed in a family of patents filed by Solexa (Milton, 2003; Milton 2018; Wu, 2020), a spin out company from Cambridge University, which was purchased by Illumina in 2007.

Experiments using 'hairpin' primers show the utility of the azidomethyl group in radiolabelled reversible chain terminators. In Fig. 7 (left), a schematic shows (a) incorporation of the modified nucleotide with the 3′-OH protecting group (red dot) and fluorescent label (green dot); (b) a 'chase' by native unmodified nucleotide to check incorporation of the modified nucleotide by blocking further incorporation; and (c) deprotection of the modified nucleotide to remove the blocking group. In Fig. 7 (right), the gel bands show the first two cycles of this procedure using a radiolabelled and 3′-OH protected thymine nucleotide. Incorporation of the protected nucleotide is observed (higher position of bands on the gel indicates a larger DNA molecule), with the chase step showing effective blocking. The deblocking step is successfully performed and the cycle is repeated.

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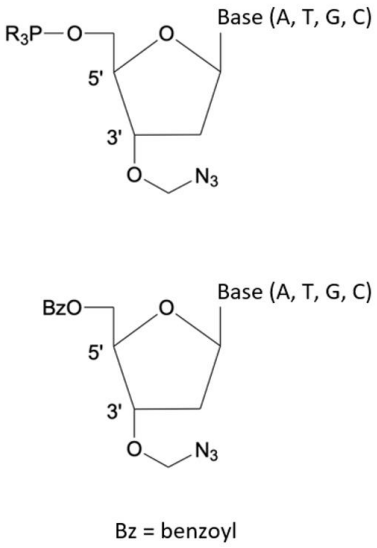

Fig. 6. *Top: Modified nucleotide. The 3′-OH azidomethyl protecting group on the ribose sugar and can be removed under neutral aqueous conditions using soluble phosphines or thiols. Middle: Nucleoside disclosed in Zavgorodny et al. Bottom: Claimant/Respondent Illumina Cambridge Limited and Defendants/Appellants Latvia MGI Tech SIA et al.*

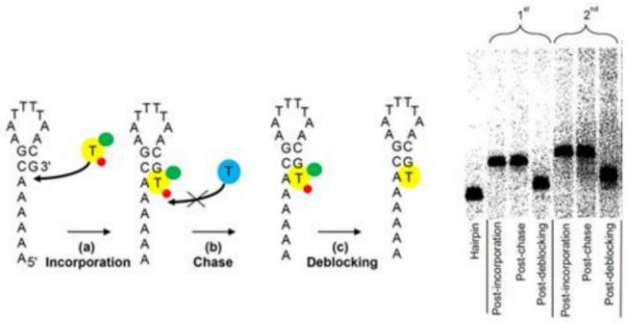

Fig. 7. *Left: Schematic of experiments showing incorporation and removal of the 3′-OH protected nucleotide. Right: Results from first two cycles of procedure.*

The Illumina patents were part of a dispute which began when MGI sought to sell DNA sequencing systems in the UK, which Illumina claimed to infringe the technology disclosed in the patents. MGI denied that the sequencing systems infringed and counterclaimed that Illumina's patents were invalid. At the High Court, it was found that Illumina's patents were valid and that MGI's systems infringed (UK 2021c).

At the Court of Appeal (UK 2021d), MGI maintained that the patents were invalid for obviousness over a paper published by Zavgorodny *et al.* (Zavgorodny 1991), which describes synthesis of substituted nucleosides (which differ from nucleotides in that they lack the 5′ phosphate group), including nucleosides with a 3′-OH protected azidomethyl group (Fig. 6).

The Court of Appeal agreed with the High Court in that whist the skilled team would consider Zavgorodny's azidomethyl protecting group for nucleosides with interest, it would only "*add to the organic chemist team member's general toolbox concerning chemical synthesis*". The skilled team, when faced with finding a suitable protecting group for a reversible chain terminator for use in DNA sequencing would still be faced with numerous possible candidates.

There are no pointers in Zavgorodny that the azidomethyl protecting group would allow nucleotide incorporation in DNA synthesis, yet alone in multiple cycles following removal of the protecting group under mild conditions. Therefore, taking into account the technical context, the Court of Appeal ruled that the High Court was correct in concluding that the skilled team, faced with the disclosure of Zavgorodny "*would read it with interest and having done so, put it down and move on*". Illumina's patents were therefore found to be inventive over Zavgorodny.

INSULET CORPORATION V ROCHE DIABETES CARE LIMITED [2021] EWHC 1933 (PAT)

Diabetes is group of metabolic diseases characterized by high glucose levels in the blood (hyperglycaemia) resulting from defects in insulin secretion, insulin action or both (DC 2010). Insulin is a hormone produced in the pancreas that controls the amount of glucose in the blood stream. The vast majority of diabetes cases fall into one of the two main categories: type 1 and type 2. Type 1 diabetes is characterized by failure of the pancreas to produce sufficient insulin and is typically due to the destruction of β-cells in the pancreas (Smith 2019; Wong 2005). In Type 2 diabetes, the cause is typically characterized by insulin resistance and a subsequent reduction in insulin secretion as the disease progresses further. In 2021, it was estimated that 537 million adults were living with diabetes and this number is predicted to rise to 643 million by 2030 and to 783 million by 2045 (IDF 2022).

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Patients with type 1 diabetes require regular blood glucose monitoring and daily insulin treatment (DUK 2022). Unlike many medicines, insulin cannot be taken orally but instead requires parental administration (injections), including the use of syringes, pens and pumps (Kesavadev 2020; Alsaleh 2010; Cobelli 2011).

Insulin pumps typically include an insulin reservoir, an infusion set or "connector" to connect the device to the body, and tubing to deliver insulin from the reservoir to the infusion set. The pump can be programmed to dispense a basal ("background") dose of insulin continuously throughout the day and night, as well as bolus doses of insulin in response to increases in blood glucose, for example at mealtimes. Insulin pumps therefore eliminate the need for multiple injections on a daily basis resulting in less insulin variation (DEO 2022).

The first prototype of an insulin pump was designed in 1963 by Dr Arnold Kadish (Kadish 1964). It was a closed-loop pump device that worked by providing continuous insulin to the body together with automatic blood glucose sensing but due to its large size it was impracticable for daily life. In 1974, Dr Ernst Friedrich Pfeiffer developed the first computer-controlled closed-loop insulin pump, named the Biostator (Pfeiffer 1974). The Biostator was able to measure blood glucose levels and dispense insulin into the body every five minutes, but its use was restricted due to being large and cumbersome (Clemens 1977).

The first wearable insulin pump known as the "autosyringe" was designed in 1976 and led to the introduction of insulin pump therapy (or Continuous subcutaneous insulin infusion (CSII)) that same year (Allen 2019). Over the years, insulin pumps have evolved to be considerably smaller and more effective, with todays so-called "smart pumps" having features such as built-in bolus calculators, personal computer interfaces, and alarms.

The patent at the heart of this dispute concerns Insulet's OmniPod® device, the first tubeless insulin pump (Fig. 98). These so called "patch pumps" are small, lightweight, and attached to the skin through an adhesive (Kesavadev 2020). The patent claimed a device and system for patient infusion (Flaherty 2007).

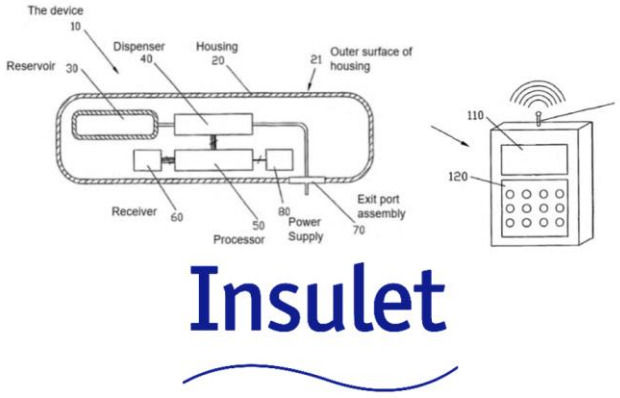

Fig. 8. *Top: Schematic of a Insulet's "patch pump" device (Fig. 1 of EP(UK)1335764). Bottom: Claimant Insulet Corporation.*

Roche began marketing its Accu-Check® Solo pump in mid-2018, three years before expiry of Insulet's patent. Insulet claimed that Roche infringed its patent directly by manufacture and sale of its kits containing the Solo pump, and indirectly by the supply of consumable components such as replacement pumps, reservoirs and remote controllers. Roche denied infringement and counterclaimed for revocation of the patent on the basis of lack of novelty, lack of inventive step and added matter (UK 2021e).

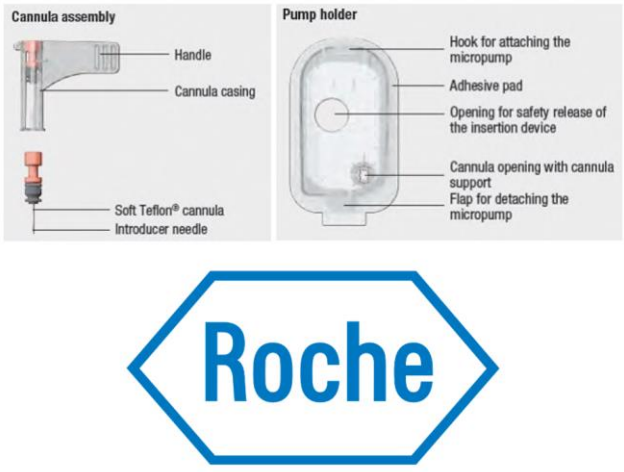

Fig. 9. *Top: Illustration of the cannula assembly and pump holder of Roche's Accu-Check Solo device. Bottom: Defendant Roche Diabetes Care Limited.*

The court first dealt with the issue of infringement. The main discussion concerned the requirement in the main claim of the patent that "*the housing is free of user input controls for providing flow instructions to the local processor*". Roche's argument was that the quick bolus buttons on the housing of its Solo device were user input controls for providing flow instructions to the local processor and therefore its device fell outside of

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the scope of the claim. Insulet's position was that the quick bolus buttons could be disabled by the user (and were likely to be disabled for significant classes of user), which would result in a device without any operable user input components on the housing as the buttons would be incapable of sending flow instructions to the local processor. The judge dismissed Insulet's argument on the basis that turning off the device did not change its function and that the quick bolus buttons were still for providing flow instructions to the local processor, even when the functionality had been disabled. On this basis, the judge found that Roche's Solo device did not infringe Insulet's patent directly or indirectly.

Roche only raised a novelty attack against the independent system claim (not the device or kit claims), and it was based on a publication referred to as "PhiScience", an international patent application for a "Portable device and method for the mobile supply of medicaments with wireless transmission of data for control or programming purposes" (Cho 2000). After concluding that PhiScience disclosed a "tubeless device", the dispute focussed on the exit port assembly (EPA) and transcutaneous patient access tool (TPAT), and specifically the integration of these features. Since neither term had a recognised technical meaning nor was defined in the patent, the judge defined an EPA as a means of connecting the flow path from the reservoir to the TPAT flow path, and a TPAT as an element that pierces the skin and enables continued transcutaneous infusion of insulin, such as a needle cannula or array of microneedles. The judge concluded that PhiScience did disclose integration between the TPAT and the EPA, and ultimately concluded that the system claim lacked novelty.

The judge went on to consider inventive step. In this case, it was agreed that the skilled team would have been led by a medical device engineer, supported by other engineers and with the benefit of input from clinicians.

Roche's case on inventive step relied on PhiScience and a second document referred to as MiniMed, an international patent application entitled "External infusion device with remote programming, bolus estimator and/or vibration alarm capabilities".

Although the judge concluded that the patent was inventive over MiniMed, the judge found all of the claims except for the kit claim to lack inventive step over PhiScience. In a further blow, Insulet were subsequently refused permission to appeal with the judge concluding that Insulet had no real prospect of success in overturning the non-infringement or invalidity findings.

CONFLICT OF INTEREST

Harry M. O'Brien is a trainee 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 personalised advice should always be sought from a licensed attorney.

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