UK High Court finds patent for Metoject® technology invalid on the ground of obviousness

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Summary

The recent UK High Court judgement in *Accord Healthcare Limited v. medac Gesellschaft [2016] EWHC 24 (Pat)* confirms the importance of seeking to "clear the way" for generic pharmaceutical companies.

In this case, Accord Healthcare Limited (Accord) sought revocation of medac Gesellschaft's (medac) patent, EP 2 046 332 (UK), on the grounds of obviousness and insufficiency. The presiding judge, Mr Justice Birss, found medac's patent to be invalid for obviousness in light of a journal article published six years before the priority date.

Introduction

This case concerned the validity of European patent EP 2 046 332 (UK), entitled "Concentrated Methotrexate Solutions". The revocation action was initiated by the generic pharmaceutical company, Accord, against the patent proprietor, medac, a German pharmaceutical company.

The patent protected medac's Metoject® syringe and pen products, which are widely used in the treatment of rheumatoid arthritis and related inflammatory conditions. Accord wanted to produce a competing injectable methotrexate product and therefore sought to clear the way for their own product launch by seeking to invalidate medac's patent.

The patent claimed the use of a formulation of methotrexate, with a concentration of about 50 mg/ml, for the treatment of inflammatory autoimmune diseases by subcutaneous injection. In high doses, methotrexate is a potent cytotoxic drug; however, in much lower doses, methotrexate has a beneficial effect in the treatment of psoriasis and rheumatoid arthritis.

Accord sought revocation of medac's patent on the grounds of obviousness in light of common general knowledge and a number of prior art documents, including the journal article "*Tolerance of parenteral, higher dose methotrexate in children with juvenile chronic arthritis*" by Russo and Katsicas (2000), Clinical and Experimental Rheumatology, Volume 18, No 3, p425, (Russo *et al.*). The patent was also asserted to be invalid on the ground of lack of sufficiency on the basis that the patent does not render it plausible that the claimed concentration of methotrexate could be safely administered to patients.

Decision

After hearing evidence from the parties' expert witnesses, Birss J concurred with Accord's submission that the relevant person skilled in the art was in fact a "team" consisting of a clinician and a pharmaceutical formulation scientist (formulator).

Birss J first considered Accord's argument for obviousness in light of Russo *et al*. Russo *et al*. reported a small clinical study in children with juvenile idiopathic arthritis that showed higher dose parenteral methotrexate

(i.e. intramuscular or subcutaneous administration) is safe and is not associated with more frequent side effects than lower dose oral administration.

The relevant aspects of Russo *et al*. concerned its disclosure relating to side effects, in particular, the pain associated with parenteral methotrexate administration. 20% of the patients on the higher parenteral dose reported "pain at injection site", although this pain was not sufficient enough for any patient to discontinue the drug. The differences between medac's patent and Russo *et al*. were that Russo *et al*. did not disclose a concentration of parenteral methotrexate and that the letter only refers to "parenteral" administration i.e. it does not identify subcutaneous administration.

After hearing evidence from the parties' expert witnesses regarding the disclosure of Russo *et al*., Birss J concluded that:

- it would be obvious for a clinician to read Russo *et al*. and embark on the creation of a formulation.
- the clinician would mention the 20% of patients that reported injection pain to the formulator in their team.
- the formulator would be aware that methotrexate had a solubility limit of up to 100 mg/ml, smaller injection volumes cause less pain and so would target an obvious small volume such as 0.5 ml.
- the formulator would realise that a higher concentration of methotrexate such as 50 mg/ml would need to be tested before it was used, but would not positively expect 50 mg/ml to be unsafe and would not be deterred from optimising.

The average parenteral dose described in Russo *et al*. is about 26 mg; to deliver 26 mg in one 0.5ml injection would require a concentration of 52 mg/ml i.e. about 50 mg/ml. Birss J was therefore satisfied that medac's patent was obvious in light of the disclosure of Russo *et al*.

Birss J then commented on the remaining obviousness arguments put forward by Accord; Birss J was particularly disapproving of Accord's attempt to argue that the invention was obvious in view of the common general knowledge alone. Birss J discussed how obviousness arguments over common general knowledge alone are generally created with hindsight knowledge of the invention and often arise when the person attacking validity has not been able to identify a piece of pertinent prior art. In this case, Birss J commented that Accord's argument of obviousness over common general knowledge alone was an attempt to "*invent as a starting point in the prior art an amalgam of the best bits of the two cited documents while leaving out the inconvenient aspects, which … created a combination which did not hitherto exist*".

Birss J concluded by discussing the squeeze between plausibility for insufficiency and obviousness, in relation to medac's assertions concerning the efficacy and side effect profile associated with the claimed use of methotrexate. The patent detailed that the reduced injection volume of methotrexate was intended to reduce pain but made no mention of the side effects of methotrexate. Birss J found that, if the claimed subject matter had been found not to be obvious because the skilled person would not have expected the claimed concentration of methotrexate to possess pain-relieving activity, then the fact that the patent did not detail the side effect profile of the drug was not material to the assessment of sufficiency If, on the other hand, a finding of non-obviousness had been based upon a purported improved side effect profile, then the absence of any information concerning the side effect of methotrexate in the patent would likely have rendered the patent insufficient.

Discussion

This case reiterates the importance of seeking to 'clear the way' for generic pharmaceutical companies. *SmithKline Beecham v. Apotex Europe [2003] FSR 30* first introduced this concept, making it incumbent upon the would-be competitor to proactively challenge patents presenting a barrier to market entry by seeking revocation and/or a declaration of non-infringement.

Although some UK court decisions following *SmithKline Beecham v. Apotex Europe* have questioned the concept of 'clearing the way' (e.g. *Cephalon Inc v. Orchid Europe [2010] EWHC 2945 (Pat)*), the present case illustrates that proactively challenging the validity of patents presenting a barrier to market entry can still play a significant role in the launch of generic pharmaceutical products.

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Legal Update

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