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A Sequel to a Relatively Unusual and Complex Patent Situation

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Re-purposing of medicines for their newer indications is a routine procedure undertaken in drug discovery, so that if successful, the regulatory approval for marketing the new use or new indication of the drug could be obtained with certainty. After the patent expiry of the older indication, generic manufacturers can begin manufacturing and marketing their version of the product for its off-patented use, if it is appropriate to do so in the country of concern. However, in certain countries, unwittingly, these generic products could also be put to a certain amount of controlling use, which is patent-protected by the innovator, in that country. When there is substantial revenue derived for the innovator from a patent for the controlling use of a drug, a relatively unusual and complex patent situation could arise. This article traces the sequel to the events in the United Kingdom covering the patented second medical indication of the drug, Pregabalin.

Keywords: Re-purposing, medicine, pregabalin, patent, controlling-use, skinny-labeling, market-protection

Letters Patent is the right conferred by a country's Patent Office to a patentee to prevent others from commercially exploiting the invention without the patentee's concurrence, during the term of the patent, in exchange for the full disclosure of the patentee's invention. Protecting a granted patent from infringement is the duty of the patentee. A recent United States Supreme Court ruling[1] held that, "a defendant's belief regarding patent validity is not a defense to an induced infringement claim." Conversely, a patentee cannot complain that his/her patent would be infringed, in anticipation of actual infringement taking place. Once the term of a patent has expired, then its exploitation falls into the public domain, for every interested person to freely use the invention, should he/she be inclined to do so. Further extension of patent protection would not be granted by a Patent Office for an expired patent, for its previously claimed use, especially one involving a medical indication.

Second Medical Use for Neuropathic Pain Treatment

It is not unusual for medicines being used in the treatment of human diseases to have more than one labeled use. This re-purposing of a drug is financially beneficial to the patentee in those countries where it is permitted, since part of the mandatory clinical data would previously have been generated during the regulatory submission to the health authorities for getting marketing approval for the older indication. Thus, for example, in the United States, a drug indicated for Paget's disease has been re-purposed for treating osteoporosis; another drug, indicated for Homozygous Familial Hyper-cholestolemia, has been re-purposed for treating Heterozygous Familial Hyper-cholestolemia; likewise, yet another drug indicated for neurodegenerative diseases has been re-purposed for treating epilepsy.[2] In this case, the drug, Pregabalin, achieved patent protection in the United Kingdom for its medical use pertaining to generalized anxiety disorder and epilepsy treatment. The patent had expired in July 2014. Subsequently, Pregabalin was also patented for its second medical indication being for the treatment of neuropathic pain, which is protected by patent in the United Kingdom until July 2017.

It is customary in the United Kingdom for doctors to prescribe a drug by its generic name, irrespective of its patent status. Interestingly, there is an unusual and complex patent situation for Pregabalin in the United Kingdom, arising from a controlling use patent, where an appeal was lodged in the Chancery Division of the High Court. In this case, the Court had decided to the effect that "...to ensure that prescribing doctors prescribe Pregabalin for the treatment of pain by reference to the brand name Lyrica omitted by the writers as this brand name is

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TM protected rather than by reference to the generic name pregabalin will ensure that pharmacists only dispense the branded product when presented with prescriptions for Pregabalin, which are (at least so far as the prescriber is concerned) for pain, without requiring the pharmacist to know the indication for which Pregabalin has been prescribed."[3] This effectively mandated that the particular product for which an old-indication patent had expired and for which a new-indication (for the same chemical compound) had been patented, be distinguished, so that one single product, Pregabalin, both for its patent-expired and for its patent-live indication required separate prescribing scripts: one generic prescription name for the off-patent use and the other proprietary prescription name for the patent-protected new use. There have been no previous examples on this scale of patent protection similar to Pregabalin's second medical use?

In March 2015, the Chancery Division of the High Court, in its opinion, encouraged Britain's National Health Service Commissioning Board (NHS) to issue guidance to prescribers regarding the appropriate name to be used for proprietary Pregabalin on a prescription. As per the judgment, only the brand name of Pregabalin which is Lyrica and not any generic equivalent name should be prescribed for patients with neuropathic pain, as long as the relevant patent is in force. Consequently, the NHS Managers had notified the General Practitioners (GPs) to prescribe Pregabalin by its brand name, when prescribing it for neuropathic pain.[4] Also, the Community Pharmacy National Negotiators of England had issued guidance to pharmacists on the Pharmaceutical Services Negotiating Committee (PSNC) regarding the requirement to dispense proprietary Pregabalin for the treatment of patients with neuropathic pain.

In the meantime, questions were being raised by health care providers in the United Kingdom, as to why they should prefer a particular brand named product, when there were many alternate suitable drugs available. Similarly, doctors were concerned about their patient's feelings of being embarrassed about their health condition of epilepsy or even anxiety, in public. It was felt by the physician community, in the United Kingdom, that privacy concerns immunized them from disclosing the reason as to why they had to prescribe Pregabalin for a patient. It was stated by the Director of Regulation and Support for the PSNC that he believed that whilst patent protection was important for stimulating the pharmaceutical industry to develop new drugs, or to extend the evidence supporting the use of existing drugs for additional indications, the second medical use patent for Pregabalin had caused considerable additional work for pharmacies and medical practices.[5]

During the second week of June 2015, an open letter to clinicians and pharmacists was sent by the innovative manufacturer of proprietary Pregabalin, which began with: "there has been some discussion and media reporting about our patent for the use of our proprietary Pregabalin for the treatment of pain over recent months. We recognize this has been the cause of concern for some of you; and we apologize if this has been the case. We hope this letter will help to bring further clarity and reassurances to all concerned."

In the United Kingdom, the above situation has caused clinicians and pharmacists to ponder about controlling-use patents and skinny-labeling situations. This situation has also caused innovator companies to ponder about data-processing requirements, which are concerned with the indications prescribed by a doctor to the commensurate prescriptions filled by a pharmacist for a given medicine. This clarification has been suggested by the innovator company, so that the correct contributory data for a drug's patented and non-patented indications, which previously were not available, could be made available in the future.

The General Practitioner Practice Prescribing Presentation-level data from February 2015 to the end of September 2015, sourced from the Health and Social Care Information Centre of the United Kingdom, states that in the United Kingdom, for the accounted time, Neuropathic pain prescription, constituted nearly 70% of Pregabalin prescriptions. The information readily available through professional literature[6], states that even for other indications, generic Pregabalin was at the relevant time, being reimbursed by the NHS at the higher patented second-medical-use-drug's price, despite alternatives being made available from January 2015. The generic manufacturers began questioning the sufficiency of the patent claim, protecting the second medical use of Pregabalin.

The Objective Indicum of the Generic Manufacturer's Mental Intention

The patentee had appealed, against the decision of the Patents Court which held that certain claims of the

European Patent (UK) No. 0,934,061 were invalid for insufficiency. The Patents Court had previously struck out the claim for infringement by the patentee against the generic manufacturer. The patentee had also appealed against the striking out of the patentee's claim for infringement of the controlling use. The Court of Appeal in the United Kingdom notes the different standards adopted by authorities of various countries to prove infringement of the second medical use patent. Some countries require "only packaging will do" approach for giving information about the controlling use patent. Some countries look for a proof of an explicit element of encouragement from the generic manufacturers, like handing-out pamphlets, advertisements etc. to doctors and pharmacists, persuading the doctors and pharmacists, to use a generic drug, for a patented-use in order to find that the manufacturers had induced infringement. Other countries look to see what steps have been put in place, by the generic manufacturers in the marketplace to prevent the use of the prohibited indication.

During their deliberations on the relevant Swiss-type second medical use claims, the judges had elaborated on the metes and bounds of infringement. Although, in a Swiss-type claimed patent, the word "for" is generally interpreted to mean *"suitable and mentally intended for"*, the judges delved deep over the phrase "the use of the drug Pregabalin " for bringing out the meaning of the word for in an objective way rather than in a subjective way. The judges of the Court of Appeal in the United Kingdom, aired their opinion in relation to the threshold proof required, to establish that the generic manufacturers had no intention to manufacture their generic Pregabalin for the purpose of infringing the controlling use patent. The judges state that, in the circumstances where the manufacturer has taken all reasonable steps within his power to prevent the infringing use of pregabalin (for treating pain), his true objective is a lawful one, and a person would be entitled to say that the foreseen consequences [of generic pregabalin being used to treat pain] were not intended, but were an unintended incident of his otherwise lawful activity. This principle recognises an obligation on the generic manufacturer, to take certain steps, if he is to enter the market, where he stands to benefit from the patentee's contribution to the art.

Conclusion

From the above September 2015 Judgment[7] of the Patents Court, it can be noted that Justice Arnold declared certain claims of the European Patent (UK) No. 0,934,061 as invalid for insufficiency. The judge had also held that the patentee's application to amend Claim 3 of the above patent after the pronouncement of judgment was an abuse of the process of the court by the patentee. The October 2016 Judgment[8] by the Court of Appeal in the United Kingdom, confirmed that Justice Arnold's conclusion on the sufficiency of the claims were correct. The Court of Appeal in the United Kingdom demarcated the role of the doctor, the dispensing pharmacist and the manufacturer of the generic drug, in contributing to the infringement of a Swiss-type claim constructed patent.

As far as the doctor's role is concerned, he could either prescribe Lyrica for the treatment of pain, in which case he would not infringe the controlling use patent, or the doctor could prescribe the generic pregabalin, in which case, the onus of infringement would rest on the dispensing pharmacist's filling of either Lyrica or Lecaent(the generic Lyrica) script. According to the Maritime and Commercial High Court of Denmark, as long as the pharmacist has not applied a label to the product for its intended use, the pharmacist has not committed a downstream act of manufacture and so has not infringed the controlling use patent[8]. Also, the pharmacist is not contributing to indirect infringement, as the manufacture of the product is complete at this stage and the product has left the manufacturer. But, if a label is applied to the product there can be direct infringement by the pharmacist and an indirect infringement by the manufacturer. This is one of the technical nuances of a Swiss-type claim.

It can be concluded that the current practice in the United Kingdom Patent Office of claiming the limitation for a pharmaceutical substance *via* a purpose-limited process claim, would subsist until the time comes for claiming its limitation *via* a purpose-limited product claim.

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