Second medical use patents and indication carve-outs

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The development of new chemical compounds (and increasingly of biologics) for the treatment of human medical ailments remains the primary focus of the world’s major pharmaceutical companies.

However, the immense cost associated with the development of new chemical entities and biologics provides great incentive for pharmaceutical companies to research new uses for existing drugs. Although there is still a substantial cost in developing a new indication for a known drug, it is proportionately far less costly than developing a new chemical entity based on original research.

Australia is one country that offers incentive in the development of new uses for known drugs by permitting such developments, that are novel and inventive, to be patented. The decision in National Research Development Corp v Commissioner of Patents (1959) 102 CLR 252 made this clear.

Against this background, this article examines:

- Second medical use patents.
- Indication carve-outs.
- The recent High Court decision in the leflunomide case.

SECOND MEDICAL USE PATENTS

There are numerous examples where new uses for known drugs have provided substantial advances in the treatment of patients:

- Thalidomide, originally developed as a hypnotic in the 1950s and subsequently taken off the market, is now being used as an immunomodulator in a variety of diseases.
- Duloxetine, a serotonin and noradrenaline reuptake blocker, developed for the treatment of depression, is being used in the management of detrusor instability.
- Buprenorphine, prescribed for control of moderate pain in low dosages, has been used for the interruption and maintenance of heroin and other opioid addictions in high dosages.
- Zoledronic acid, first used in the treatment of tumour induced hypercalcaemia, has been found to be effective against osteoporosis.

Second medical use patents present a dilemma to classical patent doctrine. Lord Hoffman (Merrell Dow v Norton [1996] RPC 76) neatly summarised the issue when he said that “ever since the power of the Crown to grant monopolies was curbed by Parliament and the courts at the beginning of the seventeenth century, it has been a fundamental principle of UK patent law that the Crown could not grant a patent that would enable the patentee to stop another trader from doing what he had done before”.

Impact of product information leaflet

In permitting patents to be granted for second medical uses of known drugs, problems can arise when a generic manufacturer is required to fully adopt the product information leaflet of the originator’s product, in order to obtain marketing approval:

- The generic company’s product information leaflet may be required to include all the medical indications for which the originator’s product is registered, including patented indications.
- This could give rise to secondary patent infringement. If the patented indication is a second medical use for a known drug product and the first use is not patented, the result may be a de facto extension of the originator’s first patent monopoly.

Hypothetical example

To take a hypothetical example:

- An originator develops and patents a compound for the treatment of tinea (compound A). The patent for compound A and the use of it in the treatment of tinea will expire after 20 years (or, if there is an extension of the patent term granted in Australia, for a period up to 25 years).
- After expiry of the patent, any generic company can market a drug containing compound A, in Australia, for the treatment of tinea (and any other non-patented indication).
- The originator company continues research and development work on compound A and subsequently discovers that it is also useful in the treatment of acid reflux.
- Assuming this new indication is not obvious, the originator can obtain a patent for the treatment of acid reflux using compound A. This method of treatment patent expires some time after the term of the original compound patent and the use of the compound for the treatment of tinea.
- The product information leaflet for the originator’s product includes both tinea and acid reflux.
- A generic company is required to adopt the originator’s product information leaflet in full. It is effectively prohibited from selling compound A at all until expiry of the acid reflux patent. This is because the product information leaflet states that the product is to be used to treat acid reflux, in infringement of the originator’s second medical use patent.
- This, in effect, gives the originator an additional exclusivity period for the underlying compound for the treatment of tinea, to which it is not entitled.

INDICATION CARVE-OUTS

The Australian Therapeutic Goods Administration requires the sponsor of a generic pharmaceutical product to include a product information leaflet with the product. This must be in substantially the same form as the product information leaflet for the originator product (section 23(2)(b) Therapeutic Goods Act 1989 (Cth) and Guidance B: Product Information, available at www.tga.gov.au).
However, it does permit the generic sponsor to "carve-out" specific indications. This practice is sometimes referred to as "skinny labelling".

Although the relevant therapeutic goods requirements permit such indication carve-outs, this does not address the legal consequences of marketing a generic with those carved-out indications.

Prescribing practices
In most countries, including Australia, medical practitioners prescribe a specific drug without reference to the indication for which it is being prescribed. Consequently, the dispensing pharmacist, when filling a prescription, will not usually know the indication for which the drug is being dispensed.

He/she will often give the patient the option of choosing a generally cheaper generic version of the drug, where available, irrespective of whether the indication for which the patient is to be treated is on the prescription.

Consequently, even where the generic sponsor has "carved out" a patented indication for a drug, there is no guarantee that the drug will not be used for a patented indication.

Second medical use claims
Although the patentability of second medical use claims has been regarded for many years as settled, a recent challenge to that position brought the issue on appeal before the High Court of Australia (Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd [2013] HCA 50) (the "leflunomide case").

In Australia, methods of medical treatment per se are patentable. There is no need to resort, for example, to Swiss-type claims, although claims of that kind are also permissible in Australia.

The more controversial issue in Australia is whether second medical uses of a known drug should be patentable, but in what circumstances is a patent for a second medical use of a known product infringed?

In Australia, there are three potential ways a patentee can argue that the supply of a generic is an infringement of a method of treatment claim:

- **Section 117 of the Australian Patents Act 1990.** This is commonly known as the "contributory infringement" section of the Patents Act.
- **Principles of joint tortfeasorship.** The company marketing the generic, by the act of supply, is aiding, inducing or procuring the infringement of the patent, by patients who use the products according to the patented method.
- **Authorisation.** The company supplying the generic is authorising the use of the product when the Patents Act gives the patentee the exclusive right to authorise others to exploit the invention during the patent term.

**Contributory patent infringement**
Section 117 of the Patents Act is a controversial part of Australia's patent legislation, and has been subject to considerable judicial scrutiny over the past two decades.

It provides that if the use of a product by a person infringes a patent, the supply of the product to that person is an infringement of the patent by the supplier, unless the supplier is the patentee or licensee of the patent (section 117(1), Patents Act). The use of a product by a person is any of the following:

- If the product is capable of only one reasonable use, having regard to its nature or design, that use (section 117(2)(a), Patents Act).
- If the product is not a staple commercial product, any use of the product, if the supplier had reason to believe that the person would put it to that use (section 117(2)(b), Patents Act).
- In any case, the use of the product in accordance with any instructions for use of the product, or any inducement to use the product, given to the person by the supplier, or contained in an advertisement published by or with the authority of the supplier (section 117(2)(c), Patents Act).

Although the wording of the section is not as clear as it could have been, it is reasonably apparent that the supply of a product will infringe a patent in one of three situations:

- If the product is capable of only one use and that use is an infringing one, supplying the product is an infringement.
- If the product is not a staple commercial product and the supplier had reason to believe that the person would put it to an infringing use, supplying the product for that use is infringing.
- If the supplier provides instructions for use of the product supplied, or advertises the product for a specific use or otherwise induces the use of the product so as to infringe a patent, the supply of the product is itself infringing.

In a second medical use claim, it is clear that section 117(2)(a) is not relevant as, by definition, the product is capable of more than one use.

It is highly likely that a court would conclude that the supply of a generic drug will infringe a method of treatment claim, under section 117(2)(c), if both:

- The generic is supplied in Australia, with an approved indication for the treatment of a medical condition, and the method of treatment is the subject of a granted patent.
- The product information leaflet which accompanies the generic includes the patented indication. In those circumstances the product information leaflet would amount to instructions for use of the product in an infringing manner.

The real question arises where:

- The supplier of the generic receives marketing approval for non-patented indications, carves out from the required product information leaflet the patented indication (for the second medical use) and supplies the generic only for use for non-patented indications.
- In those circumstances, can section 117(2)(b) still be relied on by the patentee to prevent supply of the generic, even where there are non-patented indications for that product?

That was the question which, ultimately, the Australian High Court recently had to answer in the "leflunomide case".

**THE LEFLUNOMIDECASE**

**Trial decision**

The leflunomide proceeding (Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd [2013] HCA 50) relevantly started as follows:

- In October 2008, Apotex consented to a preliminary injunction restraining it from supplying or offering to supply in Australia any product containing leflunomide, where Apotex had reason to believe that the product may be used for the treatment of psoriatic arthritis.
- In 2010, Apotex sought to vary the terms of the preliminary injunction order, in light of an amendment to its product information leaflet. The amendment carved out from the registered indications, psoriatic arthritis and psoriasis, so that the only indication referred to was the treatment of active rheumatoid arthritis. The application to vary the first injunction order was refused.

The application to vary the 2008 order was based on the submission by Apotex that, in light of the changes to the product information leaflet, there was no serious question to answer in...
respect of section 117(2)(b), which was relied on by Sanofi to establish infringement.

The patent in issue had a single claim, that is, "a method of preventing or treating a skin disorder, wherein the skin disorder is psoriasis, which comprises administering to a recipient an effective amount of a pharmaceutical composition containing as an active ingredient a compound of formula I or II [the compound being lefunomide]";

• Apotex submitted that its new product information leaflet made reference to active psoriatic arthritis but not to psoriasis. In those circumstances, Apotex argued that it had no reason to believe that a person would use its lefunomide product for an infringing use.

• However, the evidence at trial established that psoriasis is a diagnostic criterion of psoriatic arthritis. Nearly every person with psoriatic arthritis has or will develop psoriasis.

• The evidence therefore established that the administration of lefunomide to a person with psoriatic arthritis will treat that person’s psoriatic arthritis and psoriasis, or treat that person’s psoriatic arthritis and prevent psoriasis.

• Apotex’ approved product information leaflet instructed medical practitioners to use its lefunomide product for the treatment of psoriatic arthritis. It was therefore argued by Sanofi that the approved Apotex product information leaflet, in fact, instructs medical practitioners to use lefunomide to treat psoriasis.

• It was said to follow that Apotex must have reason to believe that the person to whom the product is supplied (by inference, a rheumatologist prescribing the product to a patient) will put Apotex’ lefunomide product to use for the treatment of psoriasis, thereby enlying section 117(2)(b) (It was held that lefunomide is not a staple commercial product).

At trial, Sanofi’s argument was accepted and the court held that Apotex was liable for contributory patent infringement, under section 117(2)(b) of the Patent Act.

Appeal

The matter went to the Full Court of the Federal Court of Australia on appeal and the appeal judgment was delivered in July 2012. The Full Court agreed with the analysis of the trial judge with respect to the application of section 117(2)(b), and dismissed Apotex’ appeal. Apotex sought leave to appeal to the Australian High Court which granted leave and allowed the appeal.

High Court judgment

As is often the case, the High Court judges delivered separate judgments that differ slightly in emphasis from one another.

On the issue of infringement, Hayne J (with whom French CJ agreed) considered that the issue of infringement has to be considered in the context of the regulatory background:

• Apotex’ product was registered on the Australian Register of Therapeutic Goods (ARTG) as indicated for rheumatoid arthritis and active psoriatic arthritis, but not psoriasis not associated with manifestations of arthritic disease.

• Their Honours considered that such a therapeutic good is separate and distinct from any other therapeutic good having different indications including, in particular, one that is indicated for the treatment or prevention of psoriasis.

Their Honours held that, in those circumstances:

• The supplier of the registered product would only have reason to believe that those to whom it supplied the product would put it to a use described in the indications for which the product was registered.

• There was, in effect, no credible evidence to establish that Apotex had reason to believe its product would be put to an infringing use, that is, to treat psoriasis not associated with arthritic conditions. Their Honours emphasised the fact that the product was registered on the ARTG with an express exclusion of that indication for its use.

Their Honours acknowledged that the administration of Apotex’ lefunomide to treat rheumatoid arthritis and active psoriatic arthritis would also be likely to relieve the patient’s psoriasis. However, they considered the Full Court’s construction of the patent claim to be correct, that is, confined to the deliberate administration of the compound to prevent or treat psoriasis.

Crennan and Kiefel JJ (with whom Gageler J agreed) put their finding of non-infringement on two separate bases.

First, their Honours referred to the fact that a person supplying the Apotex product but not using the patented method does not directly infringe the method patent. Their Honours then said “it is difficult to understand how the supply of an unpatented product, the use of which by a supplier would not infringe a method patent, can give rise to indirect infringement of a method patent by a supplier of the unpatented product from the supplier”.

This statement is itself difficult to comprehend in the context of section 117. The section emphasises the ultimate use of the product being supplied. If the ultimate use of the product is a direct infringement of a method claim, section 117 operates to deem the supply of the product to be itself an infringement of the patent, in circumstances where either the product is only capable of one use, the product is not a staple commercial product and the supplier ought reasonably to have expected the product to be used for an infringing purpose, or the supplier in effect induces or encourages the infringing use.

If the supplier uses the product supplied in accordance with the claimed method then the supplier will directly infringe the method claim. The fact that the person to whom the product is supplied is the one who uses the patented method ought not, logically, exculpate the supplier from liability, in the specific circumstances contemplated by section 117.

The second basis for non-infringement is similar to that relied on by Hayne J. Their Honours specifically referred to Apotex’ product information leaflet, which does not, in terms, instruct recipients to use the unpatented pharmaceutical substance in accordance with the patented method. They stated that “it was not shown, nor could it be inferred, that Apotex has reason to believe that the unpatented pharmaceutical substance, which it proposes to supply, would be used by recipients in accordance with the patented method, contrary to the indications in Apotex’ approved product information document”.

This rationale for the finding on infringement is evidence based. It seems to permit the possibility in other cases that, with more specific evidence of the likely use of the product, or in circumstances from which it might be inferred that such use would occur, infringement may be made out under section 117(2)(b).

CONCLUSIONS

The decision of the Australian High Court is unlikely to be the last word on whether indication carve-outs are an effective way for a generic pharmaceutical supplier to avoid liability for secondary patent infringement in Australia.

The lefunomide decision may be confined to its own facts. In future cases, where there is more specific evidence of prescribing practices and the ultimate use of a generic, from which an inference of direct infringement can be drawn, a different conclusion might be reached on the application of section 117(2)(b).

The outcome of any such future case will also turn on the construction given to the asserted patent claim or claims. In the lefunomide case, a narrow construction was given to the claim.

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This effectively requires an enquiry to be made into the object or end, in view of the method of treatment involving the administration of a compound in issue.

Patent claims must be given purposive construction in Australia consistent with the context provided by the patent specification. There is no universal principle of construction which will apply to all patent claims protecting the second medical use of a known drug.

Although some life has been breathed into indication carve-outs as a non-infringement strategy in Australia following the lefunomide case, they are by no means a universal panacea.

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- Representing Actavis Pharmaceuticals in Australian Federal Court litigation relating to rosuvastatin.
- Advising a multinational biotech company in relation to a patent enforcement strategy for a blockbuster biologic in Australia.