Société d'Avocats
9 rue Scribe
75009 Paris - France

www.aramis-law.com
T + 33 (0)1 53 30 77 00
F + 33 (0)1 53 30 77 01

SELARL au capital de 37.500 €
RCS Paris 487 629 982
Palais K 0186

July 2017

Second medical use patents: outcome of the *Pregabalin* case

The assessment of the infringement of second medical use patents is an issue French and European courts have been interested in for several years. A series of recent decisions have resulted in a number of convergence points being outlined more precisely as well as practical consequences for the stakeholders in the pharmaceutical industry. This study focuses on the subject in France and, on a broader scale, in Europe.

French and European courts have been interested in the issue of the assessment of the infringement of second medical use patents for almost 2 years. This issue has experienced recent developments in France, but also in the United-Kingdom and, very recently, in the Netherlands.

The case law on this subject matter was essentially developed through the "Pregabalin" case[1].

Pregabalin is an active compound used in the treatment (i) of certain forms of epilepsy (ii) certain forms of pain and (iii) generalised anxiety disorder.

The compound, pregabalin, was the subject of a European patent and a supplementary protection certificate having both expired in 2013.

In 1997, Warner-Lambert - since then bought out by the Pfizer Group - filed a European patent application covering a second medical indication for pregabalin: this patent discloses the use of pregabalin in the preparation of a pharmaceutical composition for the treatment of pain. This patent, number EP 0 934 061 (EP 061), will expire on 16 July 2017.

Pregabalin is marketed by Pfizer, under the brand name Lyrica. A marketing authorisation (MA) was granted to Pfizer for Lyrica in accordance with the "centralised" procedure on 6 July 2004. This MA was then extended in order to cover therapeutic indications that were not initially covered.

As protection of the data of the MAs filed for Lyrica expired on 2 July 2012, from this date on, generic manufacturers were able to apply for MAs for their own generic version of pregabalin using the abridged application procedure established by the regulation governing medicinal products in the European Union[2].

The majority of generic manufacturers filed their MA by "carving out" the therapeutic indication covered by patent EP 061.

This "carving-out" enabled generic manufacturers to be granted a MA for the generic version of pregabalin for all the therapeutic indications not covered by the Warner-Lambert's patent - namely epilepsy and generalised anxiety disorder - and to launch their generic versions under a "skinny label".

Our initial study, published in 2016, presented a comparative analysis of the different solutions chosen by national jurisdictions with regard to the regulatory framework governing medicinal products for human use. This study highlighted a certain number of divergences in the solutions chosen at national level as well as the numerous resulting uncertainties for both patent holders and generic manufacturers.

In light of several important decisions rendered in Member States since this study was published, it is now possible to bring major converging trends to light, but also persisting uncertainties.

A first permanent injunction granted in the Netherlands

The case law in Netherlands on this issue was established in a dispute opposing Novartis, holder of a patent covering the use of zoledronic acid in the treatment of osteoporosis, and the generics laboratory Sun Pharmaceuticals.

In this case, the summary of product characteristics (SmPC) and the patient information leaflet (PIL) of Sun Pharmaceuticals' generic product only referred to the therapeutic indication not covered by the Novartis patents, namely Paget's disease.

Once on the market, Sun Pharmaceuticals won a tender issued by a health insurance company for the supply of zoledronic acid. The tender did not allow participants to limit their applications only certain indications of zoledronic acid.

Under these conditions, Novartis filed a request for a preliminary injunction and an action on the merits against Sun Pharmaceuticals.

The Court of Appeal of The Hague granted the requested interim measures on the ground of indirect infringement, as pharmacists were obliged by the regulatory framework to prescribe the generic version for all indications of zoledronic acid, including those covered by the Novartis patent[3].

On the merits of the case, the Court of The Hague has just found Sun Pharmaceuticals liable, but this time on the ground of the direct infringement of the Novartis patent[4].

The Court of The Hague found, first of all, that indirect infringement of a second medical use patent is inconceivable as no action is carried out prior to the delivery of the generic

[1] *In the Netherlands, the latest decisions in this respect were rendered as part of a dispute opposing Novartis to Sun Pharmaceuticals concerning the generic version of zoledronic acid.*
[2] *For more details, see our article published in 2016: Can second medical use patents provide effective protective against generics entry?*
[3] *Court of Appeal of The Hague, 27 Jan 2015, no C/09/460540, Novartis vs Sun Pharmaceutical Industries BV.*
[4] *Court of The Hague, 14 April 2017, no 15/01813, Novartis vs Sun Pharmaceuticals BV.*

medicine. This statement is of particular significance given the different developments observed in other European jurisdictions on this issue (see. hereinafter).

The Court then established the elements that led to retain the notion of direct infringement of the patent holder's rights.

On the one hand, the Court took into consideration the practices of Dutch health professionals: infringement is retained insofar as Dutch practitioners do not specify the indication for which the medicine is prescribed, fact that the generic manufacturer could not be unaware of.

On the other hand, the Court of The Hague found that Sun Pharmaceuticals did not make the efforts required to avoid the generic version that it markets from being prescribed and delivered for the indication covered by the Novartis patent.

The review of this decision is of particular interest in light of solutions retained by other European jurisdictions.

The qualification of infringement of second medical use claims set aside

The decisions handed down in the past few months in France and the United-Kingdom seem to lay aside the debates about the qualification of infringement of second medical use claims.

There appears to be perceptible developments in the approaches of British and French judges with regard to the admission of indirect infringement of a second medical use patent

The order handed down by the interim judge of the Paris District Court on 2 December 2016[5] and the analysis conducted by Judge Floyd in the decision handed down by the Court of Appeal on 13 October 2016[6] suggest the possibility of indirect infringement of a second medical use patent.

In both decisions, the judge admitted that the supply of generic medicine to pharmacists may constitute the supply of means materialising the use of pregabalin for the therapeutic indication covered by the patent.

However, the recognition of a contributory infringement is acknowledged with levels of convictions that differ depending on the judge.

The wording of the order handed down on 2 December 2016 puts into light all the precautions taken by the French Judge with regard to the admission of a contributory infringement on the basis of Paragraph 1 of Article L. 613-4 of the Intellectual Property Code.

The interim judge states that "assuming that the supply to pharmacists [...] may constitute le supply of means that allows for the use of pregabalin for the treatment of neuropathic pain [...]". Same precaution is taken by the interim judge concerning Paragraph 2 of Article L. 613-4 of the code: "it can be accepted that medication is an everyday consumer product".

The British judge went a step further in the decision rendered on 13 October 2016 by the Court of Appeal. In the obiter dictum developed, Judge Floyd claimed there is a danger in translating indirect infringement into a requirement for a downstream act of manufacture prior to the supply of generic medicine. According to Judge Floyd, other processing steps carried out downstream may contribute to the invention: for instance, the labelling stage carried out by the pharmacist.

The British Judge therefore concludes that the claims of the Warner-Lambert's patent, considered as process claims since they were of Swiss type claims[7], may be the subject of indirect infringement.

In both cases, it is an improvement from earlier case-law. In earlier decisions, the French and British Judges had refused to qualify the infringement of patent of second therapeutic use as an indirect infringement as they considered the indirect infringement was inconsistent with the claims drafted in a Swiss-type form[8].

This development, notwithstanding the provisional (summary proceedings in France) and/or theoretical nature (obiter dictum in the United-Kingdom) of the decisions having established it, is most welcome for several reasons.

First of all, it is in accordance with the claims of second therapeutic indication retained by jurisdictions of other Member States.

German[9] and Danish[10] courts have had the opportunity to recognise that infringement of second medical use claims may be qualified as acts of indirect infringement.

In that regard, Judge Floyd has had the opportunity to say that the position adopted by Danish jurisdictions should be followed.

In the decision of 26 June 2015, the Copenhagen Maritime and Commercial Court issued an injunction against 220 pharmacists to stop the delivery of generic versions of pregabalin for the treatment of pain.

By doing so, the Danish Judge recognised the fact that pharmacists dispensing a generic version for an indication covered by a patent may be liable of acts of infringement.

This evolution marks the end of a preconception on the qualification of breach of patents of second therapeutic indication claims.

According to the British position, as formulated prior to the decision of 13 October 2016, indirect infringement entailed the demonstration of a downstream act of manufacture.

Yet, this condition does not appear when reading Article 60 (2) of the British Patient Act relating to indirect infringement.

Concerning the French position, the reasons for refusing to qualify the infringement of patent of second therapeutic

[5] *Paris Court of First Instance, order in summary proceedings, 2 Dec. 2016, no 16/57469, Warner-Lambert vs Sandoz, Mylan, Teva, Sanofi Generics, et a.*
[6] *Court of appeal, 13 Oct. 2016, [2016] EWCA Civ 1006, Warner-Lambert vs Actavis*
[7] *EPO, gde ch., 5 Dec 1984, no G 6/83.*
[8] *High Court of Justice (Patent Court), 10 Sept. 2015, [2015] EWHC 2548, Warner-Lambert vs Actavis. Paris Court of First Instance, order in summary proceedings, 26 Oct. 2015, no 15/58725, Warner-Lambert vs Sandoz.*
[9] *Hamburg Regional Court, 2 April 2015, Warner-Lambert vs Glenmark Arzneimittel, Aliud Pharma, 1a Pharma, Hexal.*
[10] *Copenhagen Maritime and Commercial Court, 26 June 2015, A-6-15, Warner-Lambert vs Krka et a.*

application were not laid down in the order made on 26 October 2015.

This order only stated "Sandoz companies do not provide in any way and to any third party the means to exploit in France a protected process".

From our perspective, it was also an erroneous interpretation of Paragraph 1 of Article L. 613-4 of the Intellectual Property Code.

According to this paragraph, the qualification of infringement by supply of means is dependent upon the satisfaction of 5 conditions:

- absence of consent of the patent holder on the supply of the litigious means;
- acts of supply of these means located on the French territory;
- supply of these means to a person not authorised to exploit the invention;
- supply of the implementation means for the invention relating to a crucial element of the invention;
- knowledge by a third party that the means supplied or offered by the latter are suitable and intended for the implementation of the invention.

Upon reading of these 5 conditions, there were no obstacles to qualify an infringement of a second medical claim as an indirect infringement.

It is undeniable that the generic medicine is crucial to the implementation of the invention covered by the patent of second therapeutic indication.

As for knowledge that the means delivered, namely the generic medicine, are suitable and intended for the implementation of the invention, this depends on the circumstances but cannot be excluded by principle.

This development, which arose in the latest decisions handed down on the subject matter by the French and British Judges, is the start of common grounds. It remains to be confirmed in decisions on the merits.

Standard assessment of breaches of second medical use patents

The review of the latest decisions handed down by European jurisdictions underlines a reconciliation of the standard of assessment of the infringement of second medical use patent.

In their latest statement, the French[11] and British[12] judges consider that the generic manufacturer, that took all necessary measures when launching the generic version to avoid this version being delivered for the patented indication, should not be liable for acts of patent infringement.

The British Judge presented the reasons why positive obligations were imposed on the generic manufacturer: insofar as the latter benefited from the technical contributions of the patent holder, it seems necessary to impose certain obligations.

This position is in line with the test theorised by the British Judge with regard to the assessment of direct infringement at the start of the Pregabalin case.

According to this test - qualified as a foreseeability test - infringement would be qualified if it were foreseeable to the generic manufacturer that the medicine would be used downstream by prescribing practitioners and pharmacists to treat the patented indication[13].

Introducing a notion of foreseeability in the assessment of infringement is related to the drafting of the claims of second therapeutic indication.

As these claims are drafted in the Swiss form, two elements characterise the direct infringement: on the one hand, the act in itself - namely the manufacturing, offering, marketing and selling or other of the generic product - and, on the other hand, the use for which the generic medicine is intended, namely for a patented therapeutic indication.

This test assesses, on an abstract level, what the generic manufacturer knew or could reasonably foresee when launching the medicine on the market.

On a practical level, jurisdictions take into consideration the behaviour of the generic manufacturer when launching the medicine on the market.

The latest decisions confirm this test and specify that the generic manufacturer is in a position to foresee its product shall be used for the indications covered by the patent if the necessary steps to avoid prescription or deliverance of its product for these indications are not taken.

This is also one of the factors having led the Dutch Judge, in the decision presented in this article[14].

An interesting fact to underline is that a similar test is conducted in order to assess an indirect infringement of a second medical use patent.

In the ruling of 2 December 2016, the French Judge assessed the claims raised by Warner-Lambert on the ground of indirect infringement of its patent.

The interim judge rejected the requests made on the basis of Paragraph 1 of Article L. 613-4 of the Intellectual Property Code by establishing that "all the defendant companies restricted the market authorisation to unprotected indications and clearly stated same on the leaflet included in the packaging and finally and above all, conducted an extensive information campaign addressed to pharmacists and prescribing physicians who were notified concerning all sales of the new Pregabalin generic, of the precautions to be adopted when prescribing the proprietary medicine".

The request made on the basis of Article L. 613-4 Paragraph 2 of the same Code was also rejected in the following terms: "it cannot be admitted that the defendant companies incited pharmacists or physicians to substitute generic Pregabalin for the princeps in the case of prescriptions for neuropathic pain when the latter spontaneously and fairly informed pharmacists that the market authorisation was limited to the two indications, epilepsy

[11] *Paris Court of First Instance, order in summary proceedings, 2 Dec. 2016, no 16/57469, Warner-Lambert vs Sandoz, Mylan, Teva, Sanofi Generics, et a.*
[12] *Court of appeal, 13 Oct. 2016, [2016] EWCA Civ 1006, Warner-Lambert vs Actavis.*
[13] *Court of appeal, 28 May 2015, [2015] EWCA Civ 556, Warner-Lambert vs Actavis.*
[14] *Court of The Hague, 14 April 2017, no 15/01813, Novartis vs Sun Pharmaceuticals BV.*

and general anxiety, given that this widespread information campaign generated significant costs for them."

Based on the same criteria, the French Judge rejected the application made by Warner-Lambert for infringement in his decision of 26 October 2015[15].

The latest decisions handed down by European jurisdictions seem to converge towards considering that generic manufacturers have a duty to inform healthcare professionals. This action must be carried out prior to the launch and then confirmed once the launch completed.

This implies that regulatory compliance by the generic manufacturer - namely carving out in the SmPC and PIL of the generic medicine of all protected indications - does not suffice to exclude any allegation of infringement.

Furthermore, the generic manufacturer must provide proof of a proactive behaviour.

On a practical level, what are the obligations of the generic manufacturer when entering the market?

The ruling of 02 December 2016[16] provides guidelines on the behaviour expected from the generic manufacturer.

In addition to "carving out" the therapeutic indications covered by the Warner-Lambert patent, the generic manufacturers participated in a large communication campaign amongst healthcare professionals.

The French Judge takes these information campaigns into consideration both quantitatively and qualitatively.

Thus, according to the decision, Biogaran had sent information letters to over 170,000 healthcare professionals while Teva had sent over 145,000 letters and nearly 100,000 emails.

These letters and emails specified that the generic version of pregabalin only had a MA for the therapeutic indications not covered by the patent.

In these letters, the generic manufacturers incited practitioners not to prescribe nor deliver the generic version for the treatment of neuropathic pain, covered by the Warner-Lambert patent.

These letters also encouraged professionals to prescribe the original version of pregabalin, in case of doubt on the use made of the generic medicine by the patient.

The latest decisions handed down with regard to the assessment of an infringement of patent of second therapeutic indication underline two major learnings: first is the determining influence of the generic manufacturer's behaviour when assessing the infringement of the patent holder's rights; second is the enforcement of these infringement assessment test, whether the infringement is direct or indirect.

The increasing involvement of national health authorities

Whether the regulatory framework with regard to medicinal products for human use is sufficiently respectful of the rights of the holder of a patent of second therapeutic application is a question on which jurisdictions do not share the same view.

The French Judge considers that the French regulatory system cannot lead to an infringement of the patent holder's rights.

By a formulation of principle, the ruling of 2 December 2016 states: "nor it can be maintained that the French regulations on prescription and substitution automatically result in infringement of patent rights in the case of a second therapeutic use of a given molecule which is protected, whereas previous indications for the same molecule are in the public domain".

The ruling continues by listing the safeguards provided by the French regulatory framework considered "sufficient to protect the indication protected by the patent".

First, if the International Non-proprietary Name (INN) prescription is mandatory since 1 January 2015, the prescribing practitioner has the option to add the commercial name and to indicate on the prescription "non-substitutable" (French Public Health Code, art. L5125-23). The pharmacist can also question the patient on the therapeutic indication for which the medicine he is delivering will be used.

Secondly, a therapeutic indication referred to in the register of generic medicine cannot be on the list of reimbursed medecines, so that the deliverance of generic versions for the treatment of pain shall not be reimbursed.

In the absence of proof of non-compliance by professionals of current regulations reported by Warner-Lambert and Pfizer, there are no grounds for direct infringement of patent EP 061 by all generic manufacturers.

The ruling is not clear in this respect, but the potential proof of non-compliance by professionals of their regulatory obligations would not constitute an act of direct infringement of patent EP 061 for which the generic manufacturers would be liable.

On the contrary, the ruling considers that the French regulatory system acts as a conciliator between the interests of the patent holders and the generic manufacturers.

As a result, in accordance with the ruling of 02 December 2016, the French regulatory framework in relation to the prescription and deliverance of the generic versions of medicine fully respects the rights of the holder of a patent of second therapeutic application.

In his ruling of 26 October 2015[17], the President of the Paris Court of First Instance had retained a similar formulation but in relation to indirect infringement.

This solution is in contrast with many decisions taken abroad when, spontaneously or following specific judicial and administrative proceedings, healthcare authorities made decisions to adapt the regulatory framework to the issues raised by the pregabalin case.

As a result, in Italy, the health authority (AIFA), published on its Website on 5 August and 16 September 2015[18] two directives aimed at regulating the prescription and deliverance of the generic versions of the pregabalin.

[15] *Paris Court of First Instance, order in summary proceedings, 26 Oct. 2015, no 15/58725, Warner-Lambert vs Sandoz.*
[16] *Paris Court of First Instance, order in summary proceedings, 2 Dec. 2016, no 16/57469, Warner-Lambert vs Sandoz, Mylan, Teva, Sanofi Generics, et a.*
[17] *Paris Court of First Instance, order in summary proceedings, 26 Oct. 2015, no 15/58725, Warner-Lambert and Pfizer vs Sandoz.*
[18] *See AIFA, Directive, 5 August 2015.*

As per these directives:

- practitioners are under the obligation to prescribe pregabalin under the name Lyrica when treating neuropathic pain;
- the deliverance of generic versions of pregabalin for the treatment of neuropathic pain is not reimbursed by social security.

In the United-Kingdom, the High Court of Justice issued an injunction against the National Health Service to order the issue of directives that regulate the prescription and deliverance of pregabalin for the treatment of neuropathic pain[19].

These directives, published on 06 March 2015, are addressed to British prescribing practitioners on the one hand:

"When prescribing pregabalin for the treatment of neuropathic pain to patients you should (so far as reasonably possible):

a) prescribe by reference to the brand name Lyrica®; and
b) write the prescription with only the brand name "Lyrica", and not the generic name pregabalin or any other generic brand."

On the other hand, they are addressed to pharmacists:

"When dispensing pregabalin, if you have been told that it is for the treatment of pain, you should ensure, so far as reasonably possible, that only Lyrica®, the branded form of pregabalin, is dispensed. However, when dispensing pregabalin for the treatment of anything other than pain, you are not restricted to dispensing Lyrica®."[20]

In the Netherlands, the carve out policy of the Dutch Medecines Evaluation Board has given rise to a question on the interpretation of Directive 2001/83/EC to the CJEU.

On 15 January 2016, the Dutch Medicines Agency was ordered to delete the patented indications from the online versions of the full label SmPC and PIL for generic pregabalin by versions of these documents containing a carve out with regard to the patented indication[21]..

On appeal, the Dutch Medicines indicated that it will not comply with this order which is contrary to its policy – which is unique in Europe.

In light of this, the Court of appeal of The Hague referred questions to the CJEU on 4 July 2017[22]:

- Do the provisions of Directive 2001/83/EC prevent the national authorities to publish the full label SmPC and PIL in situations where the generic manufacturer has informed the authority that it will not include the patented indication in its SmPC and its PIL?
- Does it matter that the national authority requires that the generic manufacturer includes in the PIL of the final product a reference to the website of that authority on which the full label SmPC has been published?

The pregabalin case emphasised, in several Member States, the difficulties posed by the regulatory framework with regard to the rights of the patent holder.

In some States, measures were taken to adapt the regulatory framework to the problem of assessing second medical use patent when the generic manufacturer "carved out" the patented indications.

Others, like France, put forward the fact that the regulatory framework respected the rights of the patent holder while imposing positive obligations to the generic manufacturer wishing to enter the market.

The behaviour of the patentee: new element to take into consideration?

The ruling of 02 December 2016 by the French Judge appears to introduce a new element to be taken into consideration when assessing a breach to a patent of second therapeutic indication.

The Judge of summary proceedings criticised the negligence of the patentee who did not sufficiently alert the authorities of the existence of its rights.

The attitude of Warner-Lambert is criticised insofar as it "simply wrote a few letters to the ANSM (French agency for the safety of medicinal products), CEPS (Economic Committee for Health Products) and the HAS (French health authority)".

Warner-Lambert sent three letters to the ANSM prior to the entry on the market of the generic versions of pregabalin, without contacting the ANSM again once the generic medicine was on the market.

It did not either contact again the CEPS or the HAS when the generic versions of the pregabalin entered the market. More importantly, the letters sent by Warner-Lambert to the ANSM did not mention the dozens of other generic manufacturers, preparing the marketing of the generic version of pregabalin, that were later assigned by Warner-Lambert.

Furthermore, the behaviour of Warner-Lambert was criticised due to the fact all the letters addressed to the health authorities only referred to the dispute with Sandoz without mentioning the other generic manufacturers summoned by Warner-Lambert for summary proceedings.

Analysis of the behaviour of the patentee prior to bringing legal action for infringement against the generic manufacturers is one of the learnings of the ruling of 2 December 2016.

The Judge of summary proceedings had not analysed this behaviour when ruling in 2015. Nor was this behaviour analysed by other European jurisdictions.

To this extent, we may question the scope and limits of what appears to be a new element to be taken into consideration when assessing a breach to a patent of second therapeutic indication.

We shall have to wait for future decisions in order to benefit from more clarity on this particular issue.

[19] *High Court of Justice (Patent Court), 2 mars 2015, [2015] EWHC 485, Warner- Lambert c/ Actavis*
[20] *National Health Service, Directive, 6 March 2015.*
[21] *District Court of The Hague, 15 January 2016, Warner-Lambert v De Staat der Nederlanden.*
[22] *Court of appeal of The Hague, 4 July 2017, Warner-Lambert v De Staat der Nederlanden.*

Conclusion. – It is not clear whether the Pregabalin case sets an easily replicable precedent for future cases of patents of second therapeutic indication.

The particularity of pregabalin is that it covers three therapeutic indications, each of which administrable for a large spectrum of conditions and diseases. In reality, very few medical compounds still protected have such a wide array of therapeutic applications.

As a result, "carving-out" and "cross labelling" are particularly sensitive for this compound. This does not mean that all patents of second therapeutic indication will follow the same judicial path.

What remains clear is that European Judges have been given the opportunity to set out guidelines that tend to converge. Over and above the highly legal matters on direct or indirect infringement, it strikes us that judges tend to place less and less the entire responsibility on the generic manufacturers and to increasingly implicate health authorities, even the patentees themselves.

Such a development will most certainly have an educational role in the future.

Over and above, it is not unreasonable to believe that the solution to the issue of the balance of interests raised by this type of case shall not be entirely provided by the courtrooms.

Certain initiatives appear to be emerging, in particular on the technical front with the development of information technology tools for prescribing practitioners and pharmacists that may, in time, limit the risks of "cross labelling". Naturally, the responsibility of the costs related to these tools remains a dominant issue.

Finally, it is to be hoped that a new convergence of regulatory frameworks in relation to generic medicine emerges, at least on a European scale.

Benjamin May
Partner
Aramis

Mickaël Da Costa
Associate
Aramis