

## Second Medical use Patents for Medicinal Products in the EU: When is Being Skinny not enough?

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### Introduction

As compound patents and regulatory data protection for medicinal products expire, pharmaceutical companies often rely on second medical use patents covering a second indication for a medicinal product - in order to protect their inventions and research investment. However, the question arises as to the extent of the protection that these patents offer where the compound patent has expired, and how far a generic company must go to ensure that a product authorised for indications that are not patent protected is not prescribed or supplied for an indication that is protected. This article, prepared by the members of Conference Bleue, a network of European law firms [1] specialising in pharmaceutical, health care and medical law, discusses the current position across the EU.

### Regulatory Background

As a general rule, the competent authorities seek consistency between the summary of product characteristics (SmPC) and other product information of a generic medicinal product, and that of the original, reference medicine. The EU regulatory authorities do not concern themselves with patents, and authorisations are granted based on public health considerations only, without prejudice to any relevant IP and, therefore, the ability of the holder of the authorisation to exploit it without infringing the IP of a third party.

However, Article 11 of Directive 2001/83/EC [2] permits (but does not require) a generic applicant to carve out from their SmPC any indications or dosage forms that are protected by patents to avoid infringing the second medical use patents of originator products; this is known as “skinny labelling”. It is, therefore, for the applicant to decide whether he wishes to retain the patented indications/ forms in his product label and either wait for the patent to expire before launching, or to launch at risk of infringement proceedings or to “clear the path” of relevant patents by bringing proceedings to invalidate the patent before the copier launches its product. Alternatively, the

applicant can inform the national authorities of the modifications needed to prepare a skinny label to take account of the patent situation in each country. [3]

### Issues Arising

The problem with this approach is that most healthcare professionals in Europe prescribe products based on experience with the originator product and their clinical judgment, regardless of a particular product's authorised indications for use. Physicians often prescribe drugs according to their generic, international non-proprietary name (INN) and the indication is rarely listed on the prescription. Therefore, a drug may be prescribed or dispensed cross-label (i.e. outside the authorised conditions of use and with reference to the full label of the originator product) in a way that infringes a second medical use patent, if the product is otherwise considered to be the same as the originator product. There are also differences in prescribing and dispensing practices in the EU, as well as in reimbursement of medicinal products, which means the environment is far from uniform across the EU.

EU Courts have adopted different approaches to interpreting such patents, and in considering how far a generic company must go to ensure its product does not infringe. Until recently, there has been limited case law that assesses how second medical use patents should be enforced, and what has to be shown to prove infringement. However, over the last few years, litigation has taken place across the EU, in particular relating to Pfizer's product pregabalin.

### The Case of Pregabalin

Warner-Lambert, part of the Pfizer group of companies, holds the patent for the active ingredient pregabalin, contained in its product Lyrica, which is authorised to treat a number of conditions, such as epilepsy, generalised anxiety disorder and neuropathic pain. The compound patent for Lyrica expired in 2013. However, Warner-

Lambert also holds a second medical use patent for the use of pregabalin in neuropathic pain.

After expiry of the compound patent and regulatory data protection period, generic companies across the EU applied for generic products with skinny labels, carving out the patented indication. However, litigation arose concerning how far the generic company had to go to prevent infringing use and ensure its product was used only in the carved out indications, and was not used for neuropathic pain.

## Denmark: Bruun and Hjele

In Denmark, physicians are generally required to prescribe by brand name [4]. However, a substitution scheme obligates pharmacies to dispense a cheaper, generic version of the prescribed product, if available [5].

Under the scheme, the Danish Medicines Agency (DKMA) establishes substitution groups for medicinal products with the same active ingredient in related pharmaceutical forms. If a physician prescribes a medicinal product that is part of a substitution group, pharmacies are required to offer the patient the cheapest medicinal product in the substitution group. This is subject to a few exceptions, namely if the physician has expressly indicated on the prescription that the prescribed product should not be substituted [6]. The system has been used in Denmark since November 1991. Until 2015 the rules did not take second medical use patents into account. Consequently, the pharmacies were obligated to dispense a cheaper generic product even if the prescription was for an indication protected by a second medical use patent and the generic product did not include that indication in its labelling.

However, a court decision relating to pregabalin changed this situation. In June 2015, the Danish Maritime and Commercial Court ruled that dispensing in line with the substitution scheme was a violation of patent regulation, and all Danish pharmacies were enjoined from dispensing the generic pregabalin products for the treatment of pain [7].

Immediately following the decision, the DKMA issued a notice to doctors and pharmacies that the generic versions of pregabalin could not be dispensed for the treatment of pain, and at the same time removed Lyrica from the pregabalin substitution group. With effect from November 2015, the substitution scheme was amended so that products subject to a second medical use patent would not be included in a substitution group [8]. However, unless the prescription has been issued for the treatment of the patented indication, the pharmacy must still dispense the cheapest generic version of the product from the relevant substitution group [9]. The DKMA notifies the pharmacies about products subject to this regulation.

## France: PDG Avocats

According to the French Public Health Code, doctors have to prescribe medicinal products by INN [10] and pharmacists have to dispense the generic product [11] (unless the originator product is specifically noted on the prescription). In relation to pregabalin, Sandoz obtained approval for a generic version that carved out the still patent protected indication from the marketing authorisation. In addition, Sandoz informed French doctors and pharmacists that its generic product could not be prescribed and dispensed for the treatment of pain. However, based on market share data relating to the

sale of the generic product, Pfizer claimed that Sandoz would nevertheless infringe Pfizer's patent.

In a decision dated 26 October 2015 [12] the Court of First Instance of Paris rejected the preliminary injunction application made by Warner-Lambert Company and Pfizer against Sandoz to prevent the product being used for neuropathic pain. The Court considered that there was no direct or indirect patent infringement by Sandoz. Sandoz had respected its obligations in the terms of its authorisation, and information was sent to French doctors and pharmacists. Warner-Lambert and Pfizer had not proved that Sandoz induced doctors and pharmacists to prescribe and dispense its generic product for the patented indication. Sandoz had not, therefore, infringed the patent. In addition, the Court stated that the French rules on prescription by INN, and the fact pharmacists should dispense the generic product; do not automatically lead to infringement of a second medical use patent.

In practice, therefore, in France it is difficult to avoid a generic product being prescribed and dispensed for a patented second medical use.

## Greece: M and P Bernitsas

Physicians must prescribe medicinal products using the products' INN [13]. There are certain limited exceptions to this general rule set out in the legislation, however, such exceptions concern very limited groups of products based on international standards and optimum clinical practice, and do not relate to first or second medical use patents.

The percentage of prescriptions written using the brand name cannot exceed 15% of the total value of prescriptions made annually by each physician, and the legislation provides for the maximum percentage of exceptions from the total number of prescriptions in order to protect specific groups of patients, and for consistency in the treatment of special and chronic diseases.

Physicians are obliged to select the appropriate medicinal product, in line with the therapeutic protocols of the National Medicines Organisation (EOF) and based on the characteristics, indications and information available about the active substance. Pharmacists are obliged to dispense the cheapest available medicinal product on the Greek market that meets the prescription, or, in the case of a shortage of that product, to dispense the next cheapest available medicinal product. If the patient chooses a more expensive medicinal product with the same active substance, the patient must pay, in addition to their standard contribution (if any), any difference between the insurance price of the cheapest medicinal product and the retail price of the product chosen.

The obligation to prescribe medicinal products based on the active substance applies to all products included in the positive list of prescription drugs. Up to now, there has been no case law from the Greek Courts on second medical use patents, or how mandatory prescription by INN should take such patents into account.

## Italy: Avvocati Associati Franzosi Dal Negro Setti

Italian doctors must prescribe by INN when treating a naïve patient or a new episode of a chronic disease. However, they can exclude generic dispensing at pharmacy level by prescribing by brand name and stating "not-substitutable" on the prescription along with a short justification. In any other case, the pharmacist is required to offer patients the cheapest product within the same group of products (the

so called “therapeutic class”) in the Transparency List approved by the Italian Agency for Medicinal products (AIFA). The National Health Service reimburses the cost of medicines up to the level of the cheapest product within the relevant cluster, while anything above this must be covered by patient co-payment.

In addition, skinny labelling is a mandatory rule. The Italian Code on medicinal products for human use has implemented Article 11 of the Directive by adopting stricter wording than the Directive: indications or dosage forms that are covered by a patent at the time when a generic medicine is placed on the market cannot be included in the SmPC/leaflet [14]. In relation to pregabalin, for example, the generic marketing authorisations do list neuropathic pain among the approved indications, but are subject to the condition that the labelling and SmPC carve out the patented indication. Therefore, in Italy all generic pregabalin products are marketed with skinny labels.

AIFA has been cooperative with originators holding second medical use patents in order to prevent cross-label prescription in clinical practice. In relation to pregabalin, for example, the risk of substitution and dispensing of the generic product was real because generic products and Lyrica are listed in the same cluster of the Transparency List. Upon the request of Pfizer, AIFA has, therefore, instructed physicians and pharmacists that: (i) generic pregabalin should be prescribed and/or subject to substitution at pharmacy level only for use in the unpatented indication; and (ii) the patient is entitled to full reimbursement (i.e. no co-payment) when Lyrica is prescribed for the patented indication, pain. Significantly, the software for e-prescription has also been adapted so that, for the neuropathic pain indication, the system shows Lyrica as the only permitted option. It is also interesting to note that the Italian Association of Pharmacists, Federfarma, instructed its affiliates on how to handle uncertain situations such as prescriptions reading “pregabalin+[generic brand] Note 4”. “Note 4” means that it is intended for the pain indication, and in that case, the pharmacist must call the prescribing doctor to explain that, because of the “Note 4” reference, he is obliged to dispense Lyrica.

### Norway: Haavind

There is no case law in Norway dealing specifically with the issue of second medical use patents. The Norwegian Medicines Authority has, however, implemented a procedure whereby patented indications should be marked on pharmacies’ product lists. Thus, when a (branded) pharmaceutical product is prescribed for a patented indication, pharmacies and doctors are informed that the product may not be substituted for another (generic) product.

### Portugal: Lopes Dias and Associados

The doctor must, as a general rule, prescribe all medicinal products electronically and by INN [15]. At the point of dispensing, if the medicinal product belongs to a particular therapeutic group of products, the pharmacist must comply with the prescription and offer the patient the three cheapest medicinal products within that group, unless the patient uses his right of substitution to request a different product with the same INN; if he does this, he must bear the cost of the difference in price [16].

If the medicinal product is not part of a particular group, the pharmacist must comply with the medical prescription by providing the patient with the cheapest medicinal product that meets the description of the one prescribed, again unless the patient uses his substitution right.

It is only possible for a doctor to prescribe a product using the product’s brand name in the following situations: [17]

- A proprietary medicine without a generic/similar product on the market;
- A proprietary medicine without a reimbursed generic medicine;
- Medicines that, on the grounds of intellectual property (i.e., second medical use patent), can only be prescribed for specific therapeutic indications;
- By specific justification of the prescribing doctor, where the medicine has a narrow margin or narrow therapeutic index as set out in a list approved by the medicines regulatory agency; or there is a suspicion, reported to the medicines agency, of intolerance or adverse reaction to a medicine with the same active substance marketed under another trade name; or a particular medicine is required to ensure continuity of treatment with duration longer than 28 days.

In such cases, the pharmacist must verify the prescription and the justification provided by the doctor, and dispenses the product prescribed. The patient cannot exercise any substitution right. In a case such as pregabalin, therefore, the company should notify healthcare professionals of the patent position to ensure that the branded product is prescribed for the protected indication.

### Spain: Jausas

In general, products should be prescribed by INN [18]. Where the prescription lists the INN, pharmacists must dispense the medicinal product with the lowest price within the relevant treatment group. Where the prescription states the brand name, if the medicinal product prescribed has a higher price than the lowest price of its treatment group, the pharmacist must replace the medicinal product prescribed with the medicinal product with the lowest price of its group. Therefore, doctors are entitled to prescribe the branded product for the patented use, but are under no obligation to do so. In addition, the pharmacist is obliged to substitute the branded product with a generic one if its price is higher than the one corresponding to the group price. As a result, the existence of a patented second medical use is not taken into account by the Spanish rules on prescription or dispensing.

There has been some limited case law on second medical uses, which - until very recently - tended to protect the interests of the generic company as long as the product’s labelling did not infringe the patented second medical use of the originator product.

For example, in a decision dated 16 April 2008 [19], the Court of Appeal of Madrid dismissed an injunction application made by Wyeth, who owned a patent that protected the use of venlafaxine for the treatment of anxiety disorders. The Court stated that infringement by the copier would occur if that company had obtained an authorisation that included the patented indication, or carried out other actions that promoted the use of the product in the patented indication. However, to find infringement in other circumstances would have meant the patent protection would be “enlarged” so as to reactivate the compound patent for the active substance, which had already expired.

In contrast, in a decision dated 14 April 2015 [20], the Spanish Supreme Court considered possible infringement by a generic company where the SmPC expressly contained combinations protected by the patent. The Court found that this was infringement as the company had also provided hospital staff with information on the effectiveness of its product for administration in the patented

combination, so as to enable healthcare professionals to put into effect the patented invention.

In contrast, the Commercial Court of Barcelona, in a decision of 23 June 2015 [21] in relation to pregabalin, rejected the injunction measures requested by Warner-Lambert and Pfizer on the basis that the generic companies had obtained carved out marketing authorisations, and the patented indication (i.e., pain) was not mentioned. However, this decision was overturned by the Court of Appeal of Barcelona in its judgment dated 5 July 2016 [22]. The Court of Appeal declared that the use of the skinny label was insufficient because, although the patented indication was not mentioned, there was a “real probability” that the defendants’ product would be prescribed and dispensed for the patented indication. The Decision ordered the defendants to inform customers that the product must not be prescribed or dispensed for the patented indication, and to refrain from supplying the copy product where there was reasonable evidence that it would be used for treating pain. This judgment differs from the previous Spanish case law, and states that to avoid patent infringement, is not enough to commercialise the generic product with a skinny label, but companies must also “contribute fairly to avoid the prohibited outcome”.

In light of these contradictory judgments, we must wait for future developments (such as a decision of the Supreme Court in this case) before reaching reliable conclusions on the effectiveness of second medical use patents in Spain.

### Sweden: Lindahl KB

In Sweden, generic substitution at the pharmacy level is mandatory [23]. An assessment of whether products are medically substitutable is made by the Swedish Medical Products Agency (MPA) on its own initiative [24]. This means that the company that has obtained a generic authorisation does not need to apply for such an assessment. When deciding on substitutability, according to the MPA’s interpretation of the regulations, which has been confirmed in case law, [25] the MPA is obliged to make a medical assessment and, therefore, does not take into account the existence of any patents. Nor is the decision on substitutability limited to the patent-free areas listed in the generic medicinal product’s label. A decision on substitutability, therefore, means that mandatory exchange at the pharmacy will take place even if the patient is being treated for a condition that is outside the generic medicinal product’s label and which is still patent protected. Since the Swedish reimbursement system is product-based (as opposed to indication-based), the generic medicinal product will also be reimbursed, even when its actual use is for a cross-label and patent-protected indication.

Patients will, therefore, receive the generic product that is the cheapest at the time of dispensing, regardless of the indication for which it has been prescribed. Furthermore, in the Swedish system, the prescribing doctor does not state information about the patient’s condition on the prescription, meaning that the pharmacy has no information about which indication the medicinal product will be used for. It is unclear what measures would constitute patent infringement and what steps need to be taken in order to be able to market a generic product for non-patented uses. These issues have not yet been tried by Swedish courts, but the Swedish regulatory system for generic substitution is in obvious conflict with the patent system and reasonable protection for second medical use patents.

### United Kingdom: Arnold and Porter

In England, prescriptions are generally written by INN, although there is no obligation to do so; there is no system of automatic generic substitution. The pharmacist must dispense the product that meets the specification stated on the prescription [26] - if this is the INN, the pharmacist will dispense the cheapest product, but if the prescription contains the brand name, the pharmacist must dispense that product.

There had been limited case law on how second medical use patents would be dealt with by the National Health Service, until the recent litigation on pregabalin. However, in December 2014, Warner-Lambert applied to the Court for an interim injunction in respect of Actavis’ generic pregabalin product, known as Lecaent. This requested that Actavis undertake several steps to ensure that Lecaent was not used for the pain indication, such as that the packaging for Lecaent be over-stickered to state that it should not be dispensed for pain.

However, the Court did not accept Warner-Lambert’s arguments, [27] and found in favour of the defendants. The Court of Appeal also dismissed Warner-Lambert’s appeal of this decision. However, the Court at first instance stated that it should be possible to issue guidance for doctors and pharmacists that Lecaent should not be prescribed or dispensed for the pain indication. Therefore, in February 2015, Warner-Lambert applied for, and was granted, an order requiring the National Health Service to state that where pregabalin is prescribed for the treatment of pain, the prescription must state “Lyrica” rather than the INN. This guidance was issued in February 2015.

The judgment on the substantive issues in the case was provided in September 2015 [28] where the Court found that Actavis had not infringed Warner-Lambert’s patent: the patent related to manufacture, and at the point of manufacture, Actavis did not intend, and did not foresee, that its product would be intentionally administered for the treatment of pain. In addition, there was no infringement by downstream users as they did not “manufacture” the product. The Court noted that there was limited evidence as to the extent to which the guidance had been successfully communicated to or implemented by doctors and pharmacists, and it appeared that it had not been as effective as hoped. The appeal of this decision was heard by the Court of Appeal in May 2016, but no judgment has yet been published.

As a result, the position as it currently stands, means it is hard for an originator company to prove infringement of a second medical use patent by a well-advised generic company absent some evidence that the patented indication is being deliberately targeted. In addition, the effect of guidance from the National Health Service is unclear; as such information is often ignored by physicians if there is no difference between the formulations themselves.

### Additional countries

Ireland (Arthur Cox) does not have any specific litigation in this area, and would look to the UK and the rest of Europe (including the European Patent Office) for jurisprudence on second medical use patents. Similarly, in Lithuania and Latvia (bnt Heemann Klauberg Krauklis APB), there are no official decisions or guidance on second medical use patents. Medicinal products are often prescribed, and reimbursed, by INN, without regard to the authorised indication or any relevant patents. However, some standard practices have developed based on unofficial/ unpublished decisions, and it is recommended to



coordinate with the responsible state institution to confirm the current practice.

## Conclusion

The protection of second medical use patents is currently uncertain across the EU, with the extent to which generic companies have to ensure the non-infringing use of their products interpreted differently by national courts. While some countries, such as Denmark, have adopted a pragmatic approach to ensure certainty for all parties, other countries, such as Spain, seem to have taken different approaches in different cases. It remains to be seen whether some consistency will develop as more companies seek to enforce such patents.

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