

**Clinical Innovation – Fair and Effective Incentives for New Uses of Established Drugs**  
**Conference - Pre-Read**

The aim of this note is to consider some of the issues surrounding the development of further medical uses for existing drugs and to highlight some country-specific examples of developments of interest in recent years.

**What is the Goal?**

Put simply, the goal is to benefit society as a whole by increasing the number of medicines which are available to doctors to treat patients. The number of available medicines will increase significantly if potential further uses for existing drugs are investigated and developed. Economic viability is required for pharmaceutical companies to investigate new potential uses and to develop these uses into approved medicines. Some form of incentive must be offered<sup>1</sup>. Historically, the incentives offered to pharmaceutical companies have been in the form of exclusivity periods in which to sell the medicine containing the drug for which a second medical use has been developed. An exclusivity period could be in the form of a second medical use patent (which was capable of being enforced appropriately) and/or a period of regulatory data protection or some other form of market exclusivity.

Whatever form of exclusivity is awarded for a new use for an existing drug, it must not interfere with the freedom of competition for any earlier uses for which exclusivity has expired.

**The Need for New Medicines**

Patient need for new treatments and therapies continues to grow rapidly as the expectation of a long and active life increases. However it is unrealistic to think that those growing needs can be satisfied by new drugs alone. As biological medicines gradually replace small molecules as the biggest blockbuster therapies, is it right to continue to operate under the premise that new drugs are always the answer?

**A costly and risky enterprise**

Conservative estimates price bringing a new drug to market at around US\$1 Billion. The basic economics of such an undertaking makes it inevitable that some opportunities will be

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<sup>1</sup> There is no reason why time-limited exclusivity must act as the incentive. However, other incentives such as cash lump sums are generally not considered appropriate. This is considered later in this note.

prioritised over others but even so, many of those endeavours will fail to provide safe and efficacious drugs to the patient. The prize for creating the next blockbuster is higher than ever but the cost of failing has grown in equal measure. The cost of failure has been felt right across the industry with many firms responding by consolidating expertise in particular areas of therapy, and divesting those divisions which have failed to lay a golden egg. Drug development is an expensive business so when a division ceases to be an asset it can quickly become a crippling liability.

Much of the cost involved in developing a new drug is due to the regulatory requirements; with phase 3 clinical trials alone costing hundreds of millions of dollars. On one hand we know that regulatory requirements are essential to ensuring that new drugs are effective and safe for the patients who take them. But on the other hand, putting every candidate through the full battery of regulatory reviews and testing processes is financially impossible to do. It is certainly a case of rocks and hard places but is there any way to reconcile this dilemma?

### Safety First

For ‘new’ drugs it is abundantly clear there cannot be, nor should there be, any way around the extensive regulatory requirements which currently exist: new drugs must be thoroughly tested before entering the patient population. However, where a new therapy or treatment uses an ‘old’ drug (i.e. one which has already undergone regulatory approval for a different therapeutic use) the safety of the drug has already been fully assessed under the regulatory regime and ultimately approved for human use. Furthermore, because an ‘old’ drug has often been used in the clinic for some years there will likely to be wealth of pharmacovigilance data to support the safety data contained in the original regulatory dossier.

### **Untapped Potential and Missed Opportunities**

There are many examples of existing drugs being successfully developed for new uses. For instance, finasteride was first marketed for the treatment of prostate disorders but was found to be effective in the treatment of androgenetic alopecia. Thalidomide was first developed for respiratory infections, then notoriously to relieve morning sickness in pregnant women. It was then later found also to be useful in the treatment of leprosy and much later again, cancer. Daclizumab was first used in transplant rejection but has been found to be effective in treating certain types of multiple sclerosis.

However anecdotal evidence suggests that there are still many hundreds of potential new therapeutic uses for old drugs that could address unmet medical needs which at present remain untapped whilst originator life sciences companies continue to prioritise their resources into the development of wholly new medicines.

Why are opportunities to develop new uses for known medicines being given a much lower priority by originators? In short, the answer is that the systems of most countries do not provide sufficient incentive to encourage such investment.

### **What are the Pros and Cons of Existing Incentives for the Development of Further Medical Uses?**

#### Second Medical Use patents

The law makers have long been aware of the need to encourage the development of existing drugs for new uses and have, either directly by virtue of the a legal/judicial fudge, given some sort of protection to new uses through second medical use patents. However, the question remains whether second medical use patent are the solution to this problem and, if they do not provide the complete answer, what other steps are necessary to provide sufficient incentives to pharmaceutical companies.

The patent systems of most major countries provide for some sort of patent protection for new uses for existing medicines. There are four principle types of second medical use claim:

- Method of Treatment claims – A method for treating Y comprising administering an effective amount of X (such claims are allowable in e.g. the US and Australia).
- “Swiss-type” claims – Use of X in the manufacture of a medicament for the treatment of Y (such claims were permitted in the EPO and national patent offices in Europe (up until 2011) and are routinely granted in China, Japan, and many other countries).
- “EPC-2000” claims – X for use in the treatment of Y (permitted in the EPO and national patent offices in Europe since 2011).
- German Second Medical use claims – use of X in the treatment of Y (this type of claim seems to be idiosyncratic to Germany)

However the question remains: Do patents provide the solution to the problem of incentivising the development of new uses for existing drugs?

The short answer is no. Second medical use patents do not provide the solution – at least not the whole solution, for at least the following reasons:

First, it may not be possible to obtain a patent for a new medical use at all because the use is not novel or inventive under established principles of patent law. This could be, for instance, because evidence has been published about the new use in the scientific literature. Additionally, in most countries around the world, the patentee must include some form of teaching in the specification that the second medical use is efficacious or at least a credible theory as to why the second medical use would be efficacious. Even though clinical data is not usually required, the level of data or other teaching required by different patent offices around the world varies which presents a considerable challenge to would-be patentees. Originators must wait to file their patent applications until they have enough evidence to be satisfied that it is likely that the second medical use will work but before any data is published which might potentially invalidate any patent application made based on that data. Finding the ‘sweet spot’ in which to file is at best tricky, and at worst nigh on impossible.

Additionally, patents for second medical uses are often very difficult to enforce. One reason for this is the disconnection which typically exists between the various stakeholders in the chain of supply for a medicine. In many countries, a doctor will prescribe a medicine by reference to the INN for the active ingredient in the medicine. The prescription will be fulfilled by the pharmacist without the knowledge of the use to which the medicine is to be put and generally the pharmacist will dispense a generic version of the medicine, if available<sup>2</sup>. Finally, the pharmacist will typically be reimbursed by the payor (usually the government or a private insurance company) at a fixed level regardless of whether the branded or generic version is dispensed. Thus, once generic versions of a medicine have become available in the market, a patentee stands little prospect of ensuring that only its medicine is dispensed for the patented second medical use. As will be set out below, in some countries ingenious judicial solutions to this problem have been found. However, more often than not there is an element of recommendation or guidance and the judicial ‘duct tape’ will not provide the long term solution that is needed.

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<sup>2</sup> Generally, generic versions of the medicine will be available but with the further medical use carved-out from the label. When carved-out medicines are dispensed for a patented indication, this is often referred to as “cross-label” use. This should be distinguished from true “off-label” use.

## Regulatory Data Protection

In Europe, a company which generates clinical data for a medicine is given a period of exclusivity during which time a third party is not permitted to rely on that data in support of its application for a generic version of that medicine. In Europe, the relevant period is 8 years of regulatory data protection from the grant of its marketing authorisation during which no generic company can use the data at all plus 2 years of market exclusivity during which the generics company can rely on the data to support its application for an authorisation but cannot market a product using an authorisation based on that data. In Europe, if a separate indication is developed by the originator in the 10 year period of exclusivity outlined above, the originator will be entitled to an extra one year of exclusivity in respect of that data.

In addition to, or as an alternative to, patent protection, it could be possible to incentivise originator companies to develop further medical uses for known drugs by granting them a further periods of regulatory data protection for the clinical data relating to the further uses which are developed. This would have the distinct advantage over second medical use patents in that it would compensate the originator for the investment it made regardless of whether knowledge of the second medical use or its potential was already known. However, additional data exclusivity periods alone would not solve the problem because generic medicines for the first non-exclusive use would be available and without systems which enable stakeholders in the healthcare system to differentiate between exclusive and non-exclusive uses, generic first use medicines (even without market authorisation for the new use or with carved-out labels) would in practice still be dispensed in place of exclusive use medicines for the new use. In essence a regulatory data protection solution faces many of the same problems with substitution at the pharmacy that any other 'exclusivity period' based solutions (e.g. patents) would do.

## Other Incentives?

It is possible to conceive of different incentives to ensure that further medical uses for existing drugs are developed. For instance, a cash reward could be given and that would undoubtedly be an elegant solution on one level; as no market segmentation would be needed to recover a higher reimbursement price because the innovator could receive its reward up front and without recourse to its sales of the product, while sales would be reimbursed at a single price regardless of the use. However, the level of the reward and precisely who would pay it would no doubt be contentious political issues.

Another possible solution would be for generics companies to have to pay a royalty to the originator when the generic medicine was used for the new use in the period of exclusivity. However, there are at least two problems with this solution. The first is that at present, the healthcare systems in many countries do not allow the precise use of a given medicine to be tracked with accuracy. The second is that it can be difficult for a generics company to control the use to which its medicine is put and the profit margins for generic medicines are much smaller than for protected or exclusive use medicines. If it was shown that a generic medicine had been used extensively for a protected use and the generics company had to restore the originator to the position it would have been in but for this use, it is easy to see that the generics company's profits could be wiped out very quickly as it would have only been reimbursed at the generic use rate. It is not inconceivable that it might even lose money on sales. This might result in generic pharmaceutical companies being reluctant to make their medicines available for non-exclusive uses for fear that they may be dispensed for the exclusive use, which is contrary to the overall goal of allowing free competition for old, non-exclusive uses.

As an alternative to second medical use patents and/or regulatory data protection of clinical trial data, it could be possible to create a new intellectual property right – perhaps borrowing some ideas from the orphan medicines regimes to give companies which develop further uses a period of exclusivity in which to recoup the investment made in developing the new use.

### **Can the Regulatory Requirements be Shortened for New Uses for Medicines with an Existing Track Record?**

It might also be possible to reduce the financial burden involved in obtaining authorisation for a new use for a known medicine by lightening the burden on companies to show that their medicine is safe and efficacious for the new use. If a medicine has been sold for many years for one indication then that should be taken into account when considering an application for an authorisation to sell the same medicine for a different indication. Whilst, as noted above safety is paramount and no short-cuts should be permitted that could in any way prejudice patient safety, it ought to be possible to reduce the financial burden and the time delay for seeking a further medical use.

### **How to Separate Different Uses of the Same Medicine?**

However, all solutions which require there to be an exclusive market for the new use (e.g. second medical use patents, regulatory data protection, and any other exclusive sale periods)

cannot achieve very much unless healthcare systems in individual countries allow the creation of separate markets for the same product – one market for old uses which is open to competition by all and a second market for the new use which, for a period, is exclusive to the developer of that new use. In order to achieve these separate markets, greater transparency and linkage throughout the chain is needed.

One solution might be to reimburse at the point of prescription. So rather than the exclusive use being reimbursed when a particular product is dispensed for the new use, which as discussed above is difficult to track because the pharmacist may only have a script with an INN and will not know what indication the drug is prescribed for, the reimbursement would be triggered at the point of prescription with all prescriptions for the new use being credited to the company who holds the exclusive right to market the medicine for the new use.

However, this solution would require doctors to record the indication they are prescribing a medicine in some way to generate the new use reimbursement data but it would eliminate any need to communicate that information to the pharmacist. It could also mean that patients who were being prescribed ‘*supermab*’ for its new use would not be guaranteed to be given the ‘*NovelPharma*’ product unless the doctor stipulated the ‘*NovelPharma*’ branded product on the prescription (which is much easier said than done as further discussed below).

Whatever the solution it will also be necessary to win over the hearts and minds of the mainstream media which often, at least in the UK, express outrage when an existing medicine is sold at a higher price for a new indication. The mainstream media and the general public need to be enlightened as to why it is not a matter of outrage for a tablet containing the same active ingredient to have two different prices depending on the indication for which it is used.

Some of the above issues can be illustrated by the facts of the pregabalin litigation in the UK and Denmark which are outlined below:

## **The UK Pregabalin Litigation**

The facts of the pregabalin litigation are, by and large, quite typical. Pregabalin is the active ingredient in a medicine sold under the brand name Lyrica® by Pfizer. Lyrica was first developed for use in epilepsy and generalised anxiety disorder (“GAD”) and Pfizer obtained a compound patent and SPC for the molecule. Several years later, Pfizer discovered that pregabalin could be used for the treatment of pain. Pfizer obtained a second medical use patent for the use of pregabalin in the treatment of pain.

When the exclusivity for the compound pregabalin was running out, generics companies started to obtain marketing authorisations to sell pregabalin but carved-out pain from their labels so that their medicines were only authorised to be used for epilepsy and GAD. For context, pregabalin is a drug which, in the UK, is most commonly used in primary care – i.e. it is a drug which is frequently prescribed by General Practitioners to patients. Slightly different considerations apply for drugs which are mainly prescribed and dispensed in hospitals.

In the UK, the healthcare system for prescription medicines used in primary care (i.e. outside of hospitals) is such that doctors are strongly encouraged to prescribe medicines by reference to the INN name for the drug – e.g. pregabalin, and not the brand name – e.g. Lyrica. This is because in the UK, if a brand name is stated on the prescription, then only the branded medicine may be dispensed in fulfilment of that prescription. Moreover, there is no obligation (or facility) for a physician to write the indication for which the medicine is to be used on the prescription. Therefore, when a drug is authorised to treat more than one indication, the pharmacist will often have no idea of the indication for which the medicine is to be used and may dispense any medicine which will fulfil the prescription that is presented to them. Since UK pharmacists are reimbursed at a fixed level for the medicines that they dispense and are free to source medicines from the commercial market, they will typically dispense generic medicines where possible because this will increase their financial margin on the reimbursement price.

Against the above background, Pfizer were understandably anxious that generic pregabalin medicines would be dispensed where pregabalin was prescribed for the treatment of pain, as well as for epilepsy and GAD. So Pfizer embarked on a campaign with the goal of minimising such use. As part of this strategy, Pfizer engaged with the generic pharmaceutical companies with regard to the steps that the latter should take, in addition to carving out pain from their



labels, to ensure that their medicines were not used to treat pain. When agreement could not be reached, Pfizer sought preliminary relief from English Patents Court. At the beginning of 2015, Pfizer's application was heard. In his judgment dated 21 January 2015, Arnold J. refused interim relief but noted:

*“It has increasingly been recognised over the past 30 years or so that it is important to find new uses for existing medicines. Existing medicines have the advantage that they are known compounds which have been shown to have acceptable safety profiles, and therefore need much less testing from that perspective. Experience shows that a compound which has therapeutic benefit in one application not infrequently turns out to have therapeutic benefit in another application (sometimes more than one other application) which may be quite different to the first application. Thus there is significant potential and value in finding such second (and third, etc.) medical uses. Discovering such second medical uses requires difficult and expensive research, however. How is such research to be funded? The answer which has been provided by the European patent system is to grant patents for second (and subsequent) medical uses of known compounds. The monopoly thus conferred on the inventor who finds the second medical use provides the return on the investment required to fund the research.”*

Picking up on the idiosyncrasies of the UK system for prescription medicines summarised above, Arnold J. suggested a solution to the problem whereby the markets for epilepsy/GAD on the one hand and pain on the other could be segregated. His solution involved a change to the way doctors prescribed pregabalin by prescribing by reference to the INN for epilepsy/GAD but by reference to brand name Lyrica when pain was to be treated. His solution only required a change to the prescribing behaviour by the physician and the rest would follow with the pharmacist being obliged to dispense Lyrica if that was what the script said.

In March 2015, in response to an Order of the UK court on an application for interim relief by Pfizer, the UK's National Health Service (NHS England) issued guidelines<sup>3</sup> as envisaged by Arnold J in relation to prescribing and dispensing pregabalin, those guidelines required that, in as far as was reasonably possible:

- pregabalin for neuropathic pain should be prescribed by reference to the brand name Lyrica and not with INN pregabalin or any generic brand name
- pregabalin for anything other than pain should be prescribed by reference to the INN pregabalin

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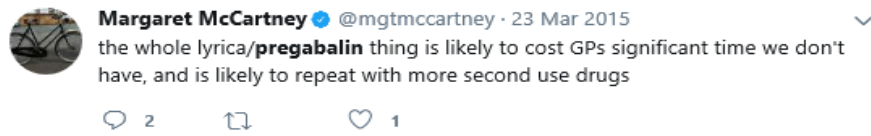
<sup>3</sup> The March 2015 NHS Guidelines were subsequently withdrawn by NHS England after the Lyrica neuropathic pain second medical use patent was found to be invalid by a judgment from the English Court of Appeal dated 13 October 2016.

- when dispensing pregabalin if the told that it is for the treatment of pain, only to dispense Lyrica.

While articles in the UK medical press, such as the British Medical Journal, adopted a more balanced factual approach to the subject; the NHS England guidelines were criticised by members of the UK medical profession on social media. Many



complained of anti-competitive behaviours or greediness on the part of Pfizer while others thought that doctors in the UK were simply too busy to prescribe by



indication. It is clear that doctors in the UK do not appreciate their right to prescribe medicines in accordance with their professional judgment being fettered, least of all by lawyers.

It seems that the NHS Guidelines ordered by the Court were only partially successful. More than six months after the Guidelines were implemented, Pfizer introduced evidence into the English Court to suggest that prescribing by reference to the INN “pregabalin” was still occurring for all indications.

The NHS England guidance in the Lyrica case raises several interesting points – could prescription guidelines be a solution to the problem? Should the physician be responsible for prescribing the appropriate product for each indication? In terms of an overall solution to the problem, issuing case by case prescribing guidelines is far from ideal for any of parties concerned. Not only do they represent an inefficient way to achieve market separation between generic and new uses by necessitating judicial intervention in every instance; one can also imagine the farcical situation developing where a physician must first cross-check against a collage of NHS England guidance pinned to her wall before writing a prescription.

### **The Danish Pregabalin Litigation**

The Danish courts wrestled with the issues surrounding the enforcement of second medical use patents following Pfizer’s request for a Preliminary Injunction (“PI”) against the leading generics manufacturer, Krka, and the Danish pharmacies to prevent cross-label use generic pregabalin for the treatment of pain. Pfizer sought a PI to prevent Krka from selling its generic pregabalin product without “ensuring” that it was not distributed and/or dispensed for the

treatment of pain. The Court noted that, as the Danish Health and Medicines Authority (DHMA) considered Krka's product and Pfizer's Lyrica to be substitutable, if a doctor prescribed Lyrica, including for the treatment of pain, but Krka's product was cheaper, then the pharmacy would be obliged to dispense Krka's product.

The Court concluded that the pharmacies' dispensing of Krka's product with a label stating that it was to be used for the treatment of pain constituted direct infringement of the patent. It held there was no clear exemption from infringement for such dispensing, e.g. under the Medicines Act or the statutory Order on prescriptions, and also considered that its decision was supported by the TRIPS Agreement. The Court therefore granted a PI against the pharmacies enjoining them from dispensing Krka's product for the treatment of pain. This decision was not appealed by the pharmacies, as the DHMA decided to withdraw substitution for pregabalin as a result of the Court's decision.

Then on 5 November 2015 the DHMA introduced Section 38a into the Order on Prescriptions to take into account patent-protected indications in the regulation of mandatory substitution of medicines. Section 38a provides:

1. *When processing a prescription for a medicinal product which – due to patent-protected indication – has not been placed in a substitution group with medicinal products which are synonymous with said medicinal product, the pharmacy shall dispense the least expensive synonymous medicinal product pursuant to the rules in section 38; however, see sub-section 2.*
2. ***If a prescription for one of the medicinal products mentioned in subsection 1 has been made out for the treatment of the patent-protected indication, the pharmacy shall dispense the medicinal product with the patent-protected indication.***
3. *The Danish Health and Medicines Authority shall inform the pharmacies when a medicinal product has a patent-protected indication; see sub-sections 1 and 2.*

Under this provision, when a pharmacy processes a prescription for a product to treat a patent-protected indication, it must dispense the patentee's product (whether that product or a Gx product was prescribed). On the other hand, if a product has been prescribed to treat a non-patented indication, mandatory substitution applies, i.e. the pharmacy must dispense the cheapest generic product. The DHMA will be responsible for informing the pharmacies about medicines with patent-protected indications, and companies that hold a patent for a specific indication are requested to inform the DHMA.

In Denmark there have also been changes to how hospital-only products are tendered for. Previously all tenders had been by active ingredient, not indication. However, AMGROS (a

public-sector organisation owned by the 5 regions responsible for the procurement of medicines for hospitals) has begun to organise separate tenders for patented and generic indications. The tenders provide that the hospitals should use the cheapest product but could use a product under the second framework contract if treatment of the patient with the cheapest product was not possible due to carved out indications. However under AMGROS' parallel frameworks hospitals are not obliged to prescribe the branded product for the patented indication.

Overall, Denmark can be seen as a country where the authorities have made significant steps towards ensuring appropriate enforcement of second medical use patents. However, these positive steps have not been replicated more widely across Europe and the rest of the world.