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Healthcare Innovation and Patent Law's 'Pharmaceutical Privilege':

Is there a pharmaceutical privilege? And if so, should we remove it?

Abstract: This article reviews current trends in patent claims regarding personalised, stratified and precision medicine. These trends are not particularly well understood by policymakers, even less by the public, and are quite recent. Consequently, their implications for the public interest have hardly been thought out. Some see personalised and other secondary drug patent claims as promoting better targeted treatment. Others are inclined to see them as manifestations of 'evergreening' whereby companies are, in some cases quite cynically, trying to extend market monopolies in old products or creating new monopolies based on supposedly improved versions of such earlier drugs. The article claims that the relaxation of 'novelty' is a privilege unavailable to inventions in other fields and that on balance the patent system does privilege this industry and that no adequate case has yet been made thus far to prove the public benefits overall.

Introduction

Patents are property rights for inventions. They are granted in exchange for public disclosure of new information concerning how to practice the invention claimed. The public may be less interested than competitors in getting that information, but what the public will supposedly gain from patents is the wider availability and circulation of useful products. At first their price is likely to be high due to the legal monopoly conferred. After patents have expired, the price of these products normally falls as competitors enter the market.

Patent law is supposedly blind with respect to labour, expense, genuinely creative thought, socio-economic significance, or to the lack of these. It is established law for well over a century that it makes no difference how the inventor came up with the invention or how

ground-breaking it may or may not be in terms of the technological or utilitarian progress it represents.¹

However, the reality belies such simplicity. Some technology fields are more equal than others. Patent law does not treat everything the same, applying uniform standards across the whole field of human creative endeavour. The pursuit of social welfare maximisation is unlikely to be adequate as a cause. Critical regulatory theories lead us to consider factors that are either intrinsic to the mechanics of the patent system itself, that are outside of the law's inner workings, or are a combination of both. Other than purely technical considerations, then, we must take into account such influences as industry lobbying, and wider government policy seeking in good faith or otherwise to promote such outcomes as enhanced innovation, investment, economic growth, or better public health, and regulatory capture.

In reality innovation in the pharmaceutical industry is a prime example of differential treatment. This article identifies certain ways that patent law appears to privilege types of pharmaceutical discovery that appear to fail at least one of the basic patentability tests. The analysis investigates the current situation with patent law in relation to current trends in commercial biomedical research including the 'personalisation turn'. The article identifies various ways that the patent system is made flexible enough to identify a wide range of discoveries, often quite minor, as being apparently inherently patentable. In doing so it calls into question the assumptions that this is good for patients and that it does not shift the balance between public and private interests too far in favour of the latter. One problem is the tendency among patent professionals and others to treat such expansive notions of inherent patentability as being entirely fair, reasonable and logical, as if any approach less favourable to commercial biomedical researchers would be unfair, unreasonable and lacking in logic.

¹ In the UK: *Crane v. Price and Others* (1842) 1 Web. 393. Similarly in the United States: *Morton v. New York Eye Infirmary* SDNY, 1 Dec., 1862.

The article argues that the generous treatment of barely inventive discoveries arising from biomedical research is in fact a privilege – in the sense of being a special right or advantage not available to all – that is based on a reinterpretation of the law reserved for this sector. As a privilege the public has both a right to confer it and a right to take it away. It follows that the onus should fall on the beneficiaries of the privilege to explain fully to the public why it should be retained, and not on the sole basis of well-practiced technical arguments. Public awareness is of course crucial in this. The public is poorly prepared to offer its views on the pharmaceutical patent privilege if it does not know the privilege exists in the first place.

Current trends in healthcare innovation, and the personalisation turn

The relationships between health, innovation and the law are dynamic and arguably changing faster now than ever before. Understanding at the molecular level of specific malfunctions which lead to disease has increased dramatically, for example in cancer. But this does not lead automatically to cures. Indeed, insights into disease causation are the start and not the end of a journey that may be long indeed. One interesting aspect of our enhanced understanding of how cellular-level malfunctions lead to disease is that some disease categories are fragmenting so that out of what was once considered a single disease arise several or many diseases. And out of one patient population sharing the same disease and treatment for it there may become several patient populations being treated for different, albeit closely related, diseases; or even patient sub-populations forming a larger population all having the same diseases but who need to be given either a completely different treatment, or a different dose or formulation of the same one.

People having the same disease can differ widely in terms of how they respond to the same treatment. Human bodies are complex enough without looking into individual human

variation. Investigating the latter alone has cost vast amounts of money and generated staggering amounts of data out of which bioinformaticians and others strive to glean patterns, connections and insights that can contribute to better healthcare. But we have far to go. It is well known that a powerful drug in a particular dosage can cure one person with minor or no side-effects, whereas the same dosage may not work on another person, cause harmful side-effects, or even endanger a patient's life. Being able to accurately predict how an individual will respond to a drug treatment and what the optimal mode of delivery should be for that person is very important, but it requires further research including the gathering of data big enough in volume and breadth of coverage to generate findings enabling precise and individualised treatment including the discovery of biomarkers.

Molecular data analysis based on genetic information acquired from large numbers of people can provide not only a massive volume of health related information, but also a diversity in the kinds of information we can derive, from responsiveness to drugs, to likelihood of contracting a particular disease, and ways to prevent or reduce risk of certain diseases later on in life. No doubt both volume and variety stand to increase tremendously in the coming years. Due to personalisation and to the sheer amount of molecular data being generated, modern day healthcare is becoming increasingly information intensive including at the personal level:

The patient is an enormous repository of information that needs to be harvested as a partnership not only in clinical care but in discovery... The ability to stratify the phenotypic expression of wellness and disease will ultimately lead to better validation of human therapeutic targets for drug discovery (Elenco, Underwood and Zohar, 2015). Much of this data is collected, stored and analysed in digital form.

The role of the drug is still central to a great deal of patient care. But prescribing a drug with a generalised instruction as to how much to take and when, is becoming insufficient. It is not just healthcare in the broad sense that is moving onto computer screens; medicine is

becoming digital as much as it is chemical, especially when treatment concerns itself ever more with disease prediction, diagnosis, prognosis, and monitoring of sickness, health and treatment effects and side-effects, and of course with personalisation. Personalised medicine is frequently held to be an exciting development that could dramatically enhance the health of millions of people. However, doubts remain that the anticipated transformative effects of personalised medicine on healthcare will all come to pass (Joyner and Paneth, 2015). Moreover, not all of this turn to big data is convenient for industry; for example, it might reveal links between a commercially successful drug and health risks for some people that would otherwise be very hard to detect. This could result in a shrinkage of the product's patient base, and even the withdrawal of the product.

Biomedical innovation is multifaceted and diverse in terms of what is being done, who is doing it and where, and it is constantly evolving. As for patenting, the subject matter of what is nowadays being claimed is hugely challenging and not necessarily easy to accommodate within the traditional product, process, and use claim categories, nor to justify in view of the function of the patent system to promote invention in the public interest.

For every Glivec, a highly effective precision medicine, there are numerous products that do little for most people who take them. A recent study showed that none of the ten bestselling drugs in the United States helps the majority of patients who are given them. In fact, they benefit only 'between 1 in 25 and 1 in 4 of the people who take them. For some drugs, such as statins – routinely used to lower cholesterol – as few as 1 in 50 may benefit' (Schork, 2015). That is really pretty staggering. The industry is raking in the cash for pretty useless products.

But is this really a low quality issue? It may be more a problem of insufficient information in two areas. First, that of not knowing anything relevant about the individual patient that would enable the tailoring of the treatment to the person. The second is that of not

knowing enough about the ‘disease’ for which the treatment is intended. A single disease may in fact be better subdivided into a series of related diseases each of which requires different therapeutic responses whether in the form of radically different drugs or alternative dosages or formulations of the same ones. If this is true, is the off-the-peg style of drug development now outmoded and ready for replacement by made-to-measure drugs? And if so, can drugs for the same disease still be cut from the same cloth or is it going to be a case of diverse treatment for different people having the same disease? As we will see in this article, the questions go beyond these rather simplistic ones. Note that I am not just talking about the science. How can firms make money from treatments that will be given to only some patients out of a much bigger population having a particular disease? And stratifying and personalising patients by drug responsiveness is not the end of it. It is no good giving the right sort of drug in the right amount to the right sort of patient if it is for the wrong sort of the disease. This is a serious issue in cancer which researchers over the years have been splitting into ever more cancers. Again, how can businesses make money from patients having a highly specific disease that is part of a ‘family’ of diseases previously thought to be one single disease?

Before going further it is important to place personalised medicine in context. Individualised medicine is one aspect of the efforts currently being made by biomedical scientists and industry to enhance targeting of disease to achieve better health outcomes for more people. Personalised medicine deals with the tailoring of treatments in a way that responds to the variability of individual human beings, and to the fact that single diseases may really be families of sub-diseases. Stratified medicine is similar except that here we focus on groups of people having shared traits that are meaningful insofar as medical intervention goes. Precision medicine is a related concept which can be seen as accommodating personalised medicine and stratified medicine in its scope. However, it implies more the idea of the ‘magic

bullet', the smart drug that forcefully hits the right target head on and without collateral damage.

Patents and commercial biomedicine

What do pharmaceutical companies patent? Nowadays, it is increasingly simplistic if not erroneous to think merely in terms of product and methods of making claims. What types of product and process claims are we talking about? What about uses? Clearly there is much more to patenting here than claiming the active ingredient of a drug and the means by which it is produced.

A treatment for disease x may turn out to be an excellent treatment for similar diseases y and z, or even for more distantly related (or unrelated) diseases d and h. This is why research continues to be done on old drugs, both successful ones and failed ones, that is, natural or synthetic chemicals that were discovered, produced and tested but which failed to work well against drug targets known about at the time. As better knowledge of cell biology, genomics and proteomics increases the number of drug targets, there is a lot of interest in testing known substances against them in the hope of discovering new therapeutic applications. Nowadays this is referred to as drug repurposing (Cragg, Grothaus and Newman, 2014; Mullard, 2012). Patent systems in many jurisdictions encourage such research by allowing claims on newly discovered medical uses of old chemical substances (see below).

Personalised and stratified medicine offer the possibility to 'save' rejected chemicals found to have some therapeutic effects across the whole spectrum of individuals suffering from a particular disease but not enough to justify further development (Allison, 2008). It seems counter-intuitive that personalised medicine is commercially attractive for industry. If we keep on splitting diseases and stratifying and personalising patients how can the industry make money? Until recently, the industry has made its biggest profits from blockbuster drugs that

are prescribed to all (or most) patients having the disease or disorder for which the drug is intended. But if the disease is in fact several diseases and a drug works effectively only against one or two of these and not all sufferers can be given the treatment anyway, the size of the market in terms of the numbers taking the drug will be much smaller. That might suggest it would not be worth developing and selling the drug. In fact, the possibility still exists to make large profits, and the patent system can potentially offer some strong legal protection for reasons that will now be explained.

Beyond product, process and use: What drug companies actually claim and what patent law permits

The pharmaceutical industry has seen a need – and been given the opportunity – to claim a wide diversity of subject matters in their attempts to protect their investments and secure legal monopoly protection with as much comprehensiveness as the law allows. Determining whether a product is new or not for the purpose of granting or refusing a patent would appear to be a fairly straightforward calculation. But this is far from being the case with medicines. Apart from the fact that the concept of novelty in patent law is largely a matter of description, specialised knowledge and public availability as opposed to whether the invention had no prior existence in any absolute sense, chemistry does present complications other types of invention do not necessarily share. A coffee lid with a useful slide to unlock mechanism aiding the retention of heat and reducing the risk of the drinker getting scalded while dashing to catch the train is novel if no such device on a coffee lid was known to exist before. The newness of a chemical composition is bound to be a lot less clear-cut and the patent system can apply novelty in a very strict way accommodating some variability or else it can be applied more narrowly. By being strict, the system might demand some additional novelty requirement so that a minor variation is disqualified because it is essentially the same thing as the disclosed

or prior art chemical it most closely relates to. If narrow, the system will accommodate only very limited variability: similar but different is different. Take two substances A and B. There is some difference of significance between them notwithstanding that they vary by one being merely purer than the other but otherwise identical, or as one being a racemic mixture comprising both left- and right-handed versions (enantiomers) of the molecule, and the other being one or other of the enantiomers. Either way, A and B can be patented as separate inventions in Europe and in the United States. Accordingly, slightly different things are treated as being something else entirely if some new difference of therapeutic or other significance is disclosed (whether or not it is proven). Minor modifications to existing medicaments such as enantiomers, combinations, and minor variants of existing products may be deemed patentable.

Generally, the system has become relaxed about novelty with respect to pharmaceuticals and this of course suits industry (albeit not the generics producers) as it was intended (see Warren-Jones (this issue) for more specific discussion on the market effects of strategic patenting enabled by the relaxed application of novelty in certain areas of chemical and pharmaceutical innovation). Purified versions of existing substances can be patented on both sides of the Atlantic and in other jurisdictions too. There are old precedents for this in the United States² and in the United Kingdom where purified insulin was patented in the 1920s. Selection inventions are also possible. The door may also be open to the patenting of naturally-occurring drug metabolites which are basically ‘made’ by the human body (see below).

There is of course a difference between the active pharmaceutical ingredient (API) and the drug product in that the tablet (if that is the mode of delivery) contains a mixture of the API and other non-active chemicals called excipients which may perform certain functions such as protecting the API on its journey through the body, controlling its rate of absorption, or enabling more convenient modes of delivery. For example, it may be possible for the same API

² Parke Davis and Co. v. H.K. Mulford and Co., 189 Fed. 95 (S.D.N.Y. 1911) affirmed, 196 Fed. 496 (2nd Cir. 1912).

to be administered in liquid rather than solid form, or can be made to be chewable so it does not have to be swallowed whole. New dosage forms, such as a pill with a known API having a new coating offering some sort of advantage, genuinely therapeutic or otherwise, are patentable.

European patent law is generally accommodating towards the pharmaceutical industry, arguably excessively so. The industry is highly organised and spends large sums of money on promoting its interests. Notwithstanding its power and influence, there are certain exclusions in terms of methods claims. As we shall see, though, these can largely be circumvented by claiming new or additional uses. There are no such statutory exceptions in the United States. European Patent Convention (EPC), Article 53(c) excludes:

(c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

The methods for treatments and diagnostic methods exclusions require some explanation in terms of their meaning, purpose and scope of application. Article 53(c)'s rationale is to immunise physicians, surgeons and veterinarians from patent infringement suits. As such it is grounded in ethics and public health concerns, though of course the industry has some grounds to consider this to be the opposite of a privilege – though as we will see ways have been found to evade it to a certain extent. This interpretation has been affirmed in a series of European Patent Office (EPO) cases.³ However, the exclusion does not extend to drugs or equipment that may be under patent.

As far as therapy goes, a line of EPO appeal board decisions has distinguished between methods intended to benefit the health of patients in a range of possible ways which fall within

³ Most notably, see G-5/83 Second medical indication/EISAI [1985], G-1/04 Diagnostic methods [2006], G-1/07 Treatment by surgery/MEDI-PHYSICS, [2011].

the exclusion, from treatments that are cosmetic in nature that do not. Cosmetic treatments are quite broad. EPO cases have found them to include methods or treatments relating to weight control, baldness and hair removal, snoring and contraception to name a few. Also falling outside the exclusion are treatments intended to kill humanely the recipient of the substance, for example euthanasia treatments for pets (but not humans).⁴

With respect to surgery, EPO cases over the years have been less consistent. But surgery is now deemed to constitute physical intervention on the body involving the application of professional medical skill and which entails substantial health risk to the subject person or animal.⁵ According to Sterckx and Cockbain (2012): ‘interventions such as massage, tattooing, tanning, shaving, ear-piercing, blood-drawing, and routine injecting or catheterisation will not classify as excluded methods of surgery’, whereas ‘bone-setting, castration, embryo implantation and cosmetic surgery involving anaesthetics seem likely to be included.’

Diagnosis necessarily involves at least two steps including data gathering or comparison followed by the act of diagnosis itself. These are all primarily mental, thus non-technical, acts that are outside of normal practice done on the body. But if diagnoses consist of ‘methods for performing mental acts’ and as such as inherently non-technical, they are not inventions anyway under EPC Article 52(2)(c). It follows that the exclusion is unnecessary. Why single out diagnostic methods for exclusion when the statutory requirements make them ineligible anyway? It is true that the Enlarged Board of Appeal decision in G-1/04 identified technical steps: those implying ‘an interaction with the human or animal body, necessitating the presence of the latter.’⁶ But this just seems like a questionable ex post facto justification for the existence of a redundant provision.

⁴ T-866/01 Euthenasia composition/MICHIGAN STATE UNIVERSITY, 2005.

⁵ G-1/07 Treatment by surgery/MEDI-PHYSICS, [2011].

⁶ G-1/04 Diagnostic methods [2006].

The EPC allows known chemicals to be patented for previously unknown uses in the above-mentioned unpatentable methods set out in Article 53(c). Providing for this (under Article 54(4)) is really a special purpose-bound exemption to the novelty provision which reflects the fact that much pharmaceutical discovery concerns extant substances, not just ones newly brought into existence by pharmaceutical chemists and designed with a specific application in mind. As such it is undoubtedly a privilege. As we will see, this is not the only relaxation of the novelty criterion provided (or permitted) in the EPC in favour of the pharmaceutical industry which appears to outweigh the dis-privilege of the provisions of Article 53(c).

The question arose of what to do about discoveries of new medical uses of substances that were already being used as medicines for something else; that is, second medical uses. Given the genuine possibility of drugs turning out to be useful for treating diseases other than the ones they were initially indicated for, the industry obviously had an interest in the patent system protecting second medical indications (NB: 'indication' in European patent law practice is more general in meaning and not confined to a specific disease or medical condition). Given that this is not product protection being sought, since of course there is no novelty there, the obstacle was the wording of Article 53(c). The 'solution' arrived at was devised by the Swiss Patent Office and became commonly known in consequence as the 'Swiss-type claim'. Accordingly, a second medical indication could side-step the methods exclusions under Article 53(c) as long as the following claim language was adopted: 'Use of a substance or composition X for the manufacture of a medicament for therapeutic application Z'. This explanatory formula for making claims was affirmed and construed broadly in a 1984 Enlarged Board of Appeal case: G-5/83 Second medical indication/EISAI. However, as from 29 January 2011, such claims are no longer accepted for new patent applications. This came after a decision of the Enlarged Board to end Swiss form claims on the grounds that they cast serious doubt –

rather damningly when one stops to think about it – on whether they fulfil novelty and inventiveness requirements (see below). Instead, a more straightforward claim is to be made: ‘Product X for use in the treatment of Z’. This is a consequence of a clause added to the revised 2000 version of the EPC which renders Swiss form claims unnecessary anyway. Article 54(5) now states that the novelty requirement:

shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in any method referred to in Article 53(c), provided that such use is not comprised in the state of the art.

That second and follow-on use claims may be under patent after the initial patent on the drug itself has expired gives rise to the following rather curious scenario: a generic version of a drug can enter the market, subject to regulatory approval, for the original indication. But if marketed for the second use, its manufacture and sale would be patent infringing. This potentially raises difficulties for national health providers, physicians and pharmacists, especially in jurisdictions in which doctors are encouraged to write prescriptions using International Nonproprietary Names (i.e. generic names) and where indications may not necessarily be entered on the prescription note. It also means that generic drug-makers must be careful about the indications they mention on the label, making sure not to include ones that are under patent protection (‘skinny labelling’). This issue is in fact central to a drawn out, complex and unresolved legal dispute between generic companies, principally Sandoz, and Pfizer concerning whether and to what extent Sandoz’s generic version of Pfizer’s Lyrica could be marketed for, prescribed and dispensed for certain medical uses disclosed in a patent in force after expiry of the initial patent granted on the compound itself. The dispute concerned not just the activities and obligations of Sandoz and other generic firms but also of pharmacies and the British National Health Service.⁷ Given the undesirability of exposing physicians and

⁷ Recent relevant decisions include *Warner-Lambert v. Sandoz and others* [2015] EWHC 3153 (Pat); *Warner-Lambert Company LLC v. Generics (UK) Ltd (t/a Mylan) & Ors* [2016] EWCA Civ 1006).

pharmacists to patent infringement suits for just doing their jobs, and here one might reflect also on the purposes of the commonly provided ‘pharmacy exemption’ written into the Agreement on a Unified Patent Court, which is likely to come into existence in 2017, this is serious cause for concern. Article 27 of this European Union instrument on limitations to rights includes ‘the extemporaneous preparation by a pharmacy, for individual cases, of a medicine in accordance with a medical prescription or acts concerning the medicine so prepared’. This is obviously not a blanket exemption for pharmacies but its inclusion in the law implies a preference for protecting them from the full weight of patent enforcement actions. It is because allowing medical indication patents entails infringement risks, not just for generic drug firms who have a vital role to play in a competitive pharmaceuticals market but also for clinicians and pharmacists, that Bostyn (2016a, b), who has considered a range of options, has advocated a broad ‘therapeutic freedom exception’, a broad immunity from infringement actions.⁸

Admittedly, there is little evidence that the pharmaceutical industry has much appetite for suing doctors or pharmacists. But pharmacists generally do not know what the medicine on a prescription is to be used for unless the patient is present to be asked and is happy to answer. One may question why they should be expected to. As mentioned, physicians may be expected to prescribe the cheaper generic version. Furthermore, they are normally permitted to prescribe medicines for known off-label uses and this is generally assumed to be in the public interest where the drugs have been properly tried and tested and proven safe through extended periods of use.

There are two other important issues. One relates to the patent incentive to invent such as it really exists, the other concerns competition. The first is part of a wider debate about whether the availability of 20-year legal monopolies for incremental inventions is a good thing

⁸ Some jurisdictions do not allow second and further medical use patents at all. For example, by virtue of the Common Regime on Industrial Property (Decision 486) Art. 21, the Andean Community of Nations (Colombia, Ecuador, Peru and Bolivia) do not allow patenting of new uses of products or processes that have already been patented.

if we would prefer to see breakthrough inventions entailing higher risk and greater investment. It should be noted here that the pharmaceutical industry tends to be regarded as the sector that is the most dependent on the patent system, and therefore for whom the patent system ought to be the most accommodating. The normal reason given is the huge and rising average costs of developing a new therapeutic chemical entity, which tends to be set against the relative cheapness of making copies whose marginal costs of production are extremely low. But this argument carries much less weight if equal 20 year monopoly rights are available also for incremental inventions whose discovery, development and marketing approval are far easier, cheaper and quicker. It may be unfair to place all the blame for the industry's conservatism on the patent system but clearly it does not seem to be helping. According to a recent article '... the human genome encodes more than 500 protein kinases, of which hundreds have been shown to have genetic links with human diseases. Yet around 65% of the 20,000 kinase papers published in 2009 focused on the 50 proteins that were the "hottest" in the early 1990s. Similarly, 75% of the research activity on nuclear hormone receptors in 2009 focused on the 6 receptors — out of the 48 encoded in the genome — that were most studied in the mid-1990s' (Edwards et al., 2011). There is an arguable case to be made that patent law is not encouraging radical innovation. The patenting of incremental innovations at the very least does nothing to change this.

With respect to competition, generic companies are able to supply the drug only for some but not all indications. This makes it harder to challenge the market power of the first entrant. If one believes in full patent rights for new medical uses that is fair enough. If one is more sceptical that this lengthy term of protection is justified for such minor discoveries, it follows that the public may not be getting the benefits it should from a truly competitive market in medicines. Studies conducted in the United States (Kapczynski et al. 2012), Australia (Moir

2016) and Switzerland (Vernaz et al. 2013) reveal that secondary patenting leads to higher prices and reduced competition due to negative effects on generic market entry.

Whereas many second use claims are targeted towards diseases and other health problems that were not previously indicated, there are further types of claim that may be allowed in some jurisdictions where the disease is actually the same as before. This is where the earlier discussion on personalised medicine becomes particularly relevant. Following the EISAI decision, claims may be allowed on further uses and methods for optimised or personalised dosage regimes, that is, for a specific schedule of doses such as take one 200 mg. tablet every six hours. This rather generous interpretation of European patent law concerning second and further use claims was reaffirmed by the Technical Board of Appeal (TBA) in Genentech/Method of administration of IFG-1 T-1020/03, [2006]. As with personalised medicine generally, there are potential advantages for industry here too: ‘increasing the number of patients who respond well to drugs while decreasing those who experience adverse effects will facilitate drug approval and make it easier for payers to reimburse for the use of the drugs’ (Peck, 2016, 145).

As an aside, it is important to differentiate between the terms ‘formulation’ when applied to a specific drug mixture in whatever type it is prepared for delivery, and a ‘dosage form’. The latter tends to refer to the physical form of the drug. Dosage forms include tablets, capsules, injectable solutions, ointments or powders to give some examples. However, the term is also used to apply to the chemical composition of the drug. Thus, there is a certain overlap in the usage of the two terms, which can be a little confusing. As we will see below, new formulations such as different mixtures containing known APIs that might offer certain advantages to patients are patentable. Examples of such patient benefits include its enabling a more convenient dosage regimen (e.g. a-one-a-day version of a drug previously to be taken

every four hours), or a reduction in side-effects. Dosage forms presented as novel and unobvious routes of administration for known drugs can also be patented (Gupta et al., 2010).

In 2008, the British Court of Appeal made an important ruling on Finasteride, which had first been patented in 1978 as a treatment for enlarged prostate. A decade later, the same company, Merck filed a patent application on the same product but for its use to treat male baldness at a daily dosage of over 5 mg. using the Swiss form of claim. In 1996 a new patent relating to the same product was granted to Merck claiming its use ‘for the preparation of a medicament for oral administration useful for the treatment of androgenic alopecia [male baldness] in a person and wherein the dosage amount is about 0.05 to 1.0 mg’. The Court, taking relevant EPO decisions into account reversed its earlier revocation, finding the new dosage regime to be novel: ‘A claim to a pill containing a 1mg dose of finasteride would be a claim to a new thing. No-one had made or proposed such a thing, so why should it not be novel?’ It was deemed non-obvious because there was deemed a low expectation of success.⁹ Ironically, it was shortly after that the EPO decided in Decision No. G02/08 - Dosage regime/ABBOT RESPIRATORY that use of Swiss-type claims should cease in light of the new language inserted into the EPC from 2000. This decision clarified two important points as follows:

1. Where it is already known to use a medicament to treat an illness, Article 54(5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness.
2. Such patenting is also not excluded where a dosage regime is the only feature claimed which is not comprised in the state of the art. [emphasis added]

Concerning personalised medicine and considering how far claims may be allowed for methods of use for something old, the following question arises: Is it possible to claim uses or

⁹ Actavis UK Ltd v Merck & Co Inc [2008] EWCA Civ 444.

methods relating to a patient population identified by a shared biomarker that forms part of a wider population of patients having the same disease and who may already have received the medicine? (Parker and Hall, 2014) Surely, if the drug has already been prescribed for that disease including to those members of the smaller population, there is no novelty. This is a tricky issue, but the EPO has allowed patents where sub-populations are clearly defined for targeting. In T-1399/04 (Combination therapy HCV/SCHERING), the TBA stated that prior public use is not necessarily novelty-destroying. Moreover, defining a group of patients medically where there is overlap with a population already receiving the same drug for the same purpose can lead to a patentable invention. As stated by the Board:

If the use of a compound was known in the treatment or diagnosis of a disease of a particular group of subjects, the treatment or diagnosis of the same disease with the same compound could nevertheless represent a novel therapeutic or diagnostic application, provided that it is carried out on a new group of subjects which is distinguished from the former by its **physiological or pathological** status.

....

According to the established case law of the Boards of appeal ..., the subject-matter ... represents a new therapeutic application as the patient group concerned is distinguishable ... by its **physiological and pathological** status. [emphasis in original]

Gaming the system? The patenting of enantiomers and other variants

Often there is a degree of variability among a class of things that many would assume practically to be identical to each other. Is a form or variant of a chemical the same thing as that chemical? Or is it something else entirely? What about drugs? While you ponder this last question, bear in mind that a pill is not just a package comprising multiple numbers of the specified active ingredient, but a collection of those plus various additional chemicals,

formulated to enhance the effectiveness of the drug product after it has entered the body. Paradoxically, it is both a pure substance and a mixture.

Let us consider one potentially significant type of variability in the pharmaceutical context: stereoisomerism. Two or more compounds may consist of the same elements in the same atomic proportions but be a different shape. The basic chemical formula is the same but each variant may interact with the human body in different ways that give rise to different effects. Isomers that are mirror images of each other are called enantiomers. A racemate is a chemical that may be one or other mirror image. Racemic mixtures tend to comprise both in equal measure, and many pharmaceutical products are such mixtures. Technically speaking, a racemate is a molecule of a certain type: it is chiral, meaning it comes in two opposite forms: left-handed and right-handed. Whether they are in the left-handed half of the mixture or in the right-handed one they do not differ in their atomic constituents. In terms of their relationship to the mixture and to their counterpart in the other half of the combination, they are referred to in chemistry-speak as enantiomers. Each may also be referred to as an optical isomer. It is possible that both enantiomers have the same therapeutic effect. But they may have very different therapeutic effects. One of the two may be toxic. In recent decades, separating enantiomers has become easier. The ability to carry out such a separation can provide genuine benefits for patients. It is much easier, as of course it should be, to acquire regulatory approval for an enantiomer than for a genuinely new chemical entity. Moreover, enantiomers are patentable. This might all appear to be reasonable, but the possibilities for ‘gaming’ the regulatory and patent systems are very much present. Chiral switching, that is, moving from the racemic mixture to an enantiomer, and filing a patent on the latter, is frequently attempted as the original patent covering the racemic mixture comes towards the end of its life.

Stereoisomerism is not the only type of variability that can be managed for commercial advantage. Prodrugs are chemically inactive drugs that are converted in the body into the active

ingredient by the action of enzymes. There are numerous reasons why prodrug forms can provide benefits, such as by enhancing in-body transportation or reducing toxicity effects. However, the actual metabolised product which causes the therapeutic effect can itself lead to an improved patient experience if delivered in that form instead. For example, the antihistamine prodrug terfenadine, marketed as Seldane, has cardio-toxic effects on some people. The metabolite, fexofenadine, subsequently marketed as Allegra (among various other names), is not. Metabolites of previously patented prodrugs can be patented too, as were both these two products. However, the situation is far from certain for companies. In the United Kingdom, the House of Lords revoked the patent on fexofenadine as the earlier patent on terfenadine had rendered it no longer novel even though the metabolite product had not been explicitly disclosed in the earlier patent.¹⁰ But this did not necessarily make it impossible to patent a metabolite given the facts of the case were specific to the patents at issue. Indeed, in a 2003 US Court of Appeals for the Federal Circuit case, Judge Rader found a metabolite to be anticipated, but went on to clarify that ‘With proper claiming, patent protection is available for metabolites of known drugs’.¹¹ He suggested different ways to evade anticipation including claiming an isolated and purified form of the metabolite or on a method of administering it to a patient.

Follow-on patents of these different kinds that claim meaningful distinctions between similar things that in other contexts might be regarded as practically identical may promise benefits for patients. For example, whereas one patented minor molecular modification to a drug may make no difference to the average patient, another could lead to a much improved therapeutic effect on at least some patients. The former type would appear to be commercially valueless. If so, why file patents on it?

¹⁰ Merrell Dow v. HN Norton (1996), Intellectual Property Reports 33:1-14.

¹¹ Schering v. Geneva Pharmaceutical, 339 F.3d 1373 (FCCA, 2003).

Notwithstanding possible benefits, patenting strategy here is clearly aimed to extend the market exclusivity of an existing drug or to support marketing aimed at switching patients to a supposedly upgraded version of a company's existing product. This is why they are controversial. Such incremental inventions may be regarded as examples of gaming the system by acquiring extended or new patent monopolies not justified by the minor level of inventive contribution or the possibly negligible added benefit to the public. Such opportunistic practices are commonly referred to as 'evergreening' (Amin and Kesselheim, 2012). The industry of course sees them as perfectly justifiable. For critics, they reflect a flaw in the patent system, one with serious implications for access to medicines, and for the promotion of innovation. If you can get 20 years' added monopoly for a modest change that may not even be an improvement relating to a product which you already enjoy a dominant market position in, why invest in more expensive and risky radical innovation?

With good marketing it may be possible to shift patients from an about to become off-patent drug onto a new version marketed under a different name that is really no better. If the original drug was successful and profitable while the patent was valid, such product switching could generate a lot of money. Some have alleged that this tactic was used by AstraZeneca. When its highly successful anti-ulcer drug omeprazole (sold as Losec, or Prilosec) was coming to the end of its patent life, and attempts to evergreen its monopoly were thwarted, the company sought to switch users to esomeprazole, branded as Nexium, a product both chemically and therapeutically virtually identical to Losec but ten times more expensive than the former drug. They did this by deploying aggressive marketing tactics claiming that it was both newer and better. Admittedly, the fact that it comprises optically pure salts of omeprazole enabled it to pass the novelty test in the key jurisdictions. But novelty in this context is a legal fiction. Like more than half of the drugs currently on the market, the active ingredient of Losec is a racemic mixture: a 50-50 mix of molecules that are mirror images of each other. Nexium is the so-called

(S) enantiomer of omeprazole, the one that is therapeutically active. Putting it another way, esomeprazole is one of two optically pure salts of omeprazole. Therefore esomeprazole was part of the contents of omeprazole.

This effort cost hundreds of million dollars in marketing, but it was worth it. ‘About 40 percent of Prilosec users made the switch to Nexium earning the drug over \$3 billion in 2003 and almost \$5 billion in 2004’ (Manners, 2006). So was Nexium any better than Losec to which it is chemically very closely related? Any improvement was modest to say the least (Angell, 2004). Apart from needing less of it to have the same therapeutic effect by dint of the fact that the other enantiomer is inactive, both Losec and Nexium are prodrugs. Both Losec and Nexium are converted into the same compound, sulfenic acid, which only has a single-handed form: it is achiral, not chiral. Therefore, whether omeprazole or esomeprazole are taken, an optically and pharmacologically identical API is formed in vivo which goes about its business in a way that does not depend on which of the two products it is derived from.

The courts are not the place to provide a definitive answer to a scientific question, but in July 2015, the Canadian Federal Court of Appeal provided an answer of sorts. The Court upheld a Federal Court decision invalidating AstraZeneca’s Nexium patent. The reason was not for lack of novelty or for obviousness, but the absence of utility.¹²

Conclusions

This article set out various approaches to fine-tuning biomedical research in ways that take account of human variability at the molecular level, and that enable a drug design methodology that ‘homes in’ on a target with greater accuracy. The patent system has generally been very supportive, among other ways by accommodating chemical, therapeutic and physiological variabilities to a fine degree and by treating novelty as a legal fiction in some areas. More

¹² AstraZeneca Canada v Apotex. 2015 FCA 158.

generally, the receptiveness of the patent system with respect to minor inventions with low inventive step and questionable novelty seem to be greater in the field of pharmaceuticals than in others. I call this ‘the pharmaceutical privilege’. It is a debateable issue whether such a privilege exists. What we can say for sure is that the patent system treats discoveries in the biomedical field differently – and largely more favourably – from those in other areas of human technical creativity. Admittedly this claim must be balanced with the existence of certain exclusions and immunities. However, it is submitted in this article that the privileges outweigh considerably the ‘dis-privileges’, and that we need to investigate whether the public gains from the patent bargain in allowing full 20-year patent rights on the incremental inventions of the kinds discussed in this article. Patents work best when they encourage inventing which would otherwise not have taken place without the ‘carrot’ of a patent, that the inventing being done is social welfare-enhancing, and that the rights are ‘strong’ enough but not excessively so. Given the point made earlier that these ‘inventions’ whose discovery and development are relatively easy, cheap and speedy as compared to a completely new drug product, it is difficult to accept that a full 20-year patent monopoly for, say, a new use or an enantiomer, is necessary. Meanwhile, it is reasonable to raise concern that such broad availability of patents either encourages the diversion of research activity towards more conservative areas, or at least that it does nothing to counter this – which is a failing.

We must of course be aware that for firms developing original products this is a highly research intensive sector. Research takes time, costs a lot of money and failures vastly outnumber the blockbuster drugs. Moreover, if we accept that the incentives for investment in innovation provided by the patent system are genuine here as elsewhere in the biomedical field, there are good arguments to justify such expansive patentable subject matter practices.

However, there are convincing counter-arguments suggesting some reining in of the scope of patentability or of the legal extent of the rights conferred would almost certainly be desirable.

One argument is based on the well-known fact that the research-based pharmaceutical industry is a master at strategic patenting practices that can be used to unjustifiably extend market exclusivity over essential medicines well beyond the life of the original patent. The greater the number of ways companies can file additional patents surrounding this or that product, the greater is the opportunity to adopt business practices that reduce competition for ever longer periods of time. Should we privilege the industry this way? While we continue to do so these legal monopolies on minor ‘tweaks’ of existing medicines and their therapeutic application, despite being unworthy of patent protection as compared to inventions in other fields where novelty is applied more strictly, unreasonably ‘lock up’ products with extended periods of legal monopoly protection. Obviously this has negative effects on patients. Competition is essential for reducing prices but it is being held back.

There are ample grounds to give serious consideration to the potential advantages of a more rigorous and consistent application of the novelty criterion to render unpatentable new discoveries of the kinds discussed earlier. This would of course leave them legally unprotected, and this may not be ideal either. Surely, we would not wish to discourage all personalised medical research, nor other modest but meaningful improvements. But we do not have to choose between extending patent protection and having no legal protection at all. Devising a limited exclusivity scheme that is narrower in scope and shorter in duration than what is normally available under the patent system seems worth considering. Another possibility is a *sui generis* system providing limited rights that would be separate from the patent system. If not rights, a reward system could be introduced instead, one that gave financial benefits proportionate to the social welfare gains but without imposing a monopoly.

The second argument was mentioned earlier: that the ease of patenting incremental inventions and the expanded market power which doing so allows discourage more radical innovation which is riskier, costs more money and takes more time to achieve. And yet the patent system does not discriminate between minor inventions on one side, protectable thanks to legal fictions (such as Nexium), and breakthrough inventions (like the original Glivec) on the other. This seems unfair and poor policy as far as the general public is concerned. Modifying the patent system giving the latter get more favourable treatment may help shift research efforts towards such areas and channel corporate marketing expenditures aimed to present the similar as radically different into actually producing the radically different.

First, though, we need to call the patent law's treatment of pharmaceutical innovation what it appears to be: a privilege, one of a few that not by chance are available in the life sciences but largely unavailable for business sectors or technological fields unrelated to biology, biomedicine or fine chemistry. It is not the only privilege in present-day patent law. For instance, isolated natural substances have been patentable for over a century in some countries despite reasonable doubts as to their novelty.

But it is a very important privilege as far as the public is concerned. By deliberately lowering novelty standards in such areas we are granting quite an unusual privilege and we should recognise it as such. There are reasons to justify doing so as there are reasons to seriously question it. What we must not do is allow people with a stake in the status quo to tell us that the present approach is technically and legally sound and that is the end of it, as if biased logic, politics and the pursuit of private interests cannot have had anything to do with it. Logical pathways leading to a legal argument are of necessity selective in terms of the factors chosen to comprise the steps taken in the thought process that leads to a given destination. Selecting one's 'staging posts' out of the same body of facts, meanings and legal principals, and drawing lines to connect the preferred ones can take you down quite different paths to very different

places. If the destination is chosen in advance, the task for legislators, lobbyists and interpreters of the law is to ensure it can be reached in a convincingly logical and reasonable manner and this is without doubt a selective mental process, one that in highly commercialised fields will suit some people's interest more than others. It may not be time to remove the pharmaceutical privilege. But it is time to review its value and if not abolish it, at least curtail it where it seems likely, on balance, to do harm to the public interest.

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