Making Medicines Affordable

Patent-related Barriers to Market Entry for Generic Medicines in the European Union

A Review of Weaknesses in the Current European Patent System and their Impact on the Market Access of Generic Medicines

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EUROPEAN GENERIC MEDICINES ASSOCIATION

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EGA
Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION
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EUROPEAN GENERIC
MEDICINES ASSOCIATION

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I. INTRODUCTION

Patents play an important role in modern society. In order to encourage the creation, dissemination and efficient exploitation of technology, patents provide inventors with a limited term legal monopoly on their invention granting them the right to exclude all others from the scope of protection offered by the patent.

Generic medicines play an equally important role in promoting pharmaceutical innovation and ensuring the affordability and sustainability of European healthcare systems. Increasing the use of generic medicines creates competition in the pharmaceutical markets which stimulates innovation, promotes cost containment, and increases access to healthcare treatments to patients. In this regard, immediate market access of generic medicines after patent expiry is of crucial interest to society, and any hurdle to this rapid access should be eliminated.

There is little doubt that patent protection is necessary in the pharmaceutical sector as upfront research and development costs are substantial. Both originator and generics participants in the pharmaceutical industry support the patent system as a cornerstone of a legislative system that seeks to provide incentives for innovation. However, the invention that sits at the centre of a patent must truly warrant the granting of a monopoly right. Once granted, abuses and the inappropriate extension of that monopoly right should be prevented.

In practice, however, a number of developments point to a strategic use of patents—of sometimes questionable quality—which is directed more toward preventing others from innovating and competing, than toward creating truly innovative products. When misused in this manner, patents can present a barrier to entry onto the generic medicines market. This report identifies some of the hurdles that generic medicines companies face in this regard in the European Union. In particular, the report focuses on the following key areas in which the patent system and the surrounding legal and regulatory framework fail to ensure an appropriate balance between incentives and competition:

1) failings in the system for granting quality patents;
2) patent thickets and follow-on patents;
3) patent litigation procedures; and
4) other patent-related barriers.

Finally, recommendations are formulated to help strike a better balance and to prevent the improper use of patents and the resultant negative effects such use has on competition from the generic medicines industry, on the development of new medicines, and on public health care in general.

II. EXECUTIVE SUMMARY

Patents are effective tools for promoting innovation in the pharmaceutical sector. Originator companies should be able to recoup their R&D investments during the term of the basic patent/SPC on an active pharmaceutical substance. Generic competition should be available immediately after expiry of that term. However, the chances of market entry for generic medicines companies in all markets the day following expiry of the main basic patent in all EU markets is not possible or, at best, is extremely difficult. Due to a diminishing number of newly registered products and contracting product pipelines, originator companies may be tempted to unjustly prolong the patent monopoly of existing products. The result is known as the 'evergreening' of a basic patent with the help of follow-on patents to keep generic competitors off the market. These follow-on patents are often weak or trivial and, upon careful examination, it is clear that they should never have been granted.

Patent quality is therefore of the utmost importance. The European patent system should only reward true inventions and should discourage patent applications for ordinary innovation. An important way of reducing the incidence of poor quality follow-on patents is to remedy certain structural deficiencies and weaknesses in the current examination procedure. Priority must be given to ensuring that the EPO has the resources it needs to continue to improve the quality of patent examiners, along with their training and remuneration, and to increase the number of more experienced senior examiners in order to give every patent application the deliberate, expert review it deserves. This would lead to a more stringent application of the patentability requirements and fewer trivial patents. Applicants should be more rigorously required to provide patent applications of the highest quality accompanied by all relevant information at the start of the examination process. Similarly, they should be under obligation to disclose all information known to them which is material to the patentability of their invention. Furthermore, better third-party participation would also help to avoid inappropriate follow-on patents from being granted. When such patents are granted, an immediate review should be possible to avoid the assertion of ultimately invalid patents to hinder generic competition. This would require an acceleration of the current opposition proceedings which today can take many years.

The structure established under the European Patent Convention only provides for a common and single European patent application and granting system by the EPO. A European patent is not a unitary patent, but essentially a bundle of national patents. As a result, questions of patent infringement and validity are governed by various national laws and are handled by the national courts operating under different procedural rules. This purely national litigation system results in a complex arena of multiple patent litigation involving high costs, forum shopping and diverging, even contradictory, court decisions. The lack of a central judiciary composed of experienced patent judges is regarded as one of the major defects in the current patent system. An effective solution would be the creation of a central European patent court that would deal with questions of invalidity and infringement at a pan-European level. Until this has been achieved, specialised national patent courts should be created with technically skilled judges with powers to reach a decision within an acceptable timeframe. Furthermore, the standard for obtaining an interim injunction should be returned to its roots as an equitable remedy since injunctions today are often used simply as a litigious tactic. This change would require a litigant to establish the existence of irreparable harm that cannot be compensated by monetary damages before a court would take the far-reaching step of enjoining a product.

Finally, measures should be taken to ensure that originator companies do not use other means to unjustly prolong their monopoly by, for example, introducing a system of patent linkage, obtaining improperly granted SPCs, deploying inaccurate marketing campaigns for promoting 'new' products with no substantial added therapeutic value as innovative products, etc. ■

III. OVERVIEW OF PATENT-RELATED BARRIERS TO GENERIC COMPETITION

1. FAILINGS IN THE SYSTEM FOR GRANTING QUALITY PATENTS

A balanced patent system requires high quality patents. This means there must be relatively little uncertainty over the breadth and validity of patent claims. The quality of a patent therefore depends on its incontestability. The existence of questionable patents creates uncertainty which leads to speculation and litigation that divert resources from research and development, stifle real innovation, and hinder generic competition, all of which in turn keeps the price of medicines unnecessarily high. An elevated standard of examination by well-trained examiners producing consistent well-considered examining results is vital to ensuring quality. However, certain structural deficiencies and weaknesses in the current examination procedure result in the grant of patents of variable quality, giving a patent owner/originator company facing expiry of a basic product patent the opportunity to create what is known as a 'patent thicket' (see below, III.2). The most obvious structural issues are discussed below.

1.1. Lack of rigorous assessment of the patentability requirements, in particular of the inventive step

One of the structural problems referred to above is that the examination of patents usually takes place under great time pressure and productivity demands despite the fact that adequate examination is of the utmost importance for patent quality. As a result, common general knowledge, especially simple textbook knowledge, is often misinterpreted, denied or neglected during examination.

> EP 690 719 (granted on 4 October 2000 and revoked on 11 May 2006) represents a striking example of this problem. EP 690 719 covered a dry mix composition of alendronic acid with lactose as diluent. A formulation closer to basic pharmaceutical knowledge is hard to imagine, but based on the international publication date, the patent created 12 years of uncertainty for competitors and it took almost six years to have it revoked. Litigation could have been commenced under this patent at any time while it was in force, leading to the difficulties discussed in section III below.

In addition, artificial problems are often presented by the patentee as needing to be 'solved' by the 'invention' in order to meet the 'problem-solution' test as applied by the European Patent Office (EPO) when evaluating the inventive step requirement. Typically solutions for problems which never existed take the form of 'new' polymorphs, particle sizes, solvent use, etc, and, in the field of pharmaceutical compositions, the use of excipients, pharmacokinetic characteristics such as dissolution rates, and formulation stability. Since no obligation exists for the patentee to submit comprehensive data about prior art, common general knowledge or comparative examples, the examiner can be easily misled.

> The application for EP 823 436 A2 is a good example of a patentee withholding information from an examiner. EP 823 436 A2 tried to obtain patent protection for both existing polymorphic forms (I and II) of finasteride. This divisional application was prosecuted for 13 years despite the fact that both forms had been disclosed in a prior research paper, but allegedly without enabling disclosure. In the end it was demonstrated by third parties that form I was the product obtained by re-working two prior art patents—EP 155 096 B1 and EP 428 366 B1—also owned by the same applicant as EP 823 436 A2. It is obvious that the originator was also aware of this fact. If no third party had taken the burden to repeat experiments described in prior art, the patent probably would have been granted (see also 1.2). The application was finally withdrawn after appeal, whereby the Board of Appeal remitted the case to the examining division.

To address patent quality, priority must be given to ensuring that the EPO has the resources it needs to continue to improve the quality of examiners, along with their training and remuneration, and to increase the number of more experienced senior examiners in order to guarantee that every patent application receives the deliberate, expert review it deserves. There is a very limited pool of people the EPO can draw from for examiners, as EPO examiners are required not only to be sufficiently qualified scientifically in a relevant technical field, but are also required to have patent training and to understand both written and spoken English, French *and* German. One way to increase this pool, and thereby to improve the technical experience of examiners, might be to accept candidates who can speak English, French *or* German—not necessarily all three—and who have better scientific qualifications in the relevant technical fields.

1.2 Lack of quality of applications/examiners' inability to check data presented to them

The onus for ensuring patent quality should not be on the EPO alone, but should instead be borne by the applicants as well. Patent quality has suffered in recent years as patent offices have been overwhelmed with an increasing volume of ambiguously worded applications for 'inventions' which often have no innovative merit. Furthermore, examiners, who are often hearing of a particular pharmaceutical for the first time, do not possess a full set of resources for assessing the validity of a patent and must rely to a great extent upon the information provided by the applicant. Examiners obviously cannot repeat experiments and do not have the same expertise as the patentee who has researched the pharmaceutical in question for an extended period of time. To help examiners overcome this limitation, the applicant should be more rigorously required to provide high quality relevant information at the beginning of the examination process, including common general knowledge (including common text books at the priority date), prior art and comparative examples.

In addition, patentees should be required to disclose full details about the experimental conditions and results which are very important for enabling a proper assessment of the invention and the inventive step. Furthermore, data with no statistical basis for proving the assertion made by the patentee should be rejected. Standard practices within the scientific community, such as quoting measuring errors, standard deviation, or confidence levels, are rarely used, but should be.

Patentees should also be held to an obligation of good faith and candour in their dealings with the EPO. Such a duty of candour exists, for example, in the United States and requires that everyone involved with a patent application must disclose all information known to them which is material to the patentability of their invention.

> The above mentioned EP 823 436 A2 application with respect to the existing polymorphic forms (I and II) of finasteride clearly shows the importance of introducing a duty of candour.

Finally, patentees should further be held accountable for the statements they make during the prosecution of their patent. This is the principle of 'prosecution history estoppel', also known as 'file-wrapper estoppel', a term used in United States patent law to indicate that a person who has filed a patent application and then makes amendments to or comments about the scope of the claim to overcome invalidity issues, has no cause of action for infringement under the doctrine of equivalents for that subject matter that was surrendered during prosecution.

1.3. Not enough consideration of third-party observations by examiners

The examination process at the EPO is primarily a dialogue between the applicant and the examiner. A system of third-party participation to catch errors and oversights in the examination process is therefore of the utmost importance. This is an inexpensive way of eliminating or adjusting the grant of a patent which may otherwise ultimately prove to be invalid. In the European examination process prior to grant, third-party observations are the only tool for parties to influence the granting procedure. The mere fact that a third party files experimental or literature data is in itself a clear indication that the patent application will have an impact on at least one other company and is, therefore, not a trivial matter. In practice, however, these third-party observations are often simply ignored by the examiner.

> The alendronate litigation matter again provides a good example. With respect to the 70mg once weekly dosage patent (EP 1 175 904), a total of four separate observations were filed. None of the points raised in the observations were taken up by the examiner and directed to the applicant for a response. The patent is now subject to 17 (!) oppositions and has been revoked in Belgium and the Netherlands (see also 2.2).

By contrast, third party observations should be taken as an opportunity by the examiner to collect useful information which would not otherwise be easily accessible. Even observations filed after acceptance of the application, but prior to grant, should be considered if the newly submitted data is highly relevant. Examination proceedings should then be reopened.

1.4. Weaknesses in the opposition procedure

The primary problem with the opposition procedure is the time taken for a decision to be reached. An obviously weak patent (for example, EP 1 169 314) can go from application to grant within 18 months. It then takes approximately four years to obtain revocation in the first instance through the EPO opposition procedure. If an appeal of that decision is lodged by the originator, it will take another three years to obtain a final decision. Pending this appeal, the decision of the Opposition Division is suspended. Calculated from the filing date, this results in nearly nine years of uncertainty. The originator has at least four years to enforce its rights from grant to the oral hearing at the Opposition Division; eventual damages to be paid in case the patent is revoked later will be offset by the lack of competition against the original product. Damage claims are rare as such claims involve costly and time-consuming legal proceedings which often do not result in a satisfactory damages award. In addition, the burden of proof shifts to the opponent during the opposition procedure. To demonstrate that something is not new and/or inventive, however, can be much more challenging and difficult to prove than the opposite.

> This point is clearly illustrated in the citalopram litigation. One of Lundbeck's follow-on patents aimed at defending its turnover from sales of Cipramil® (active ingredient citalopram hydrobromide) was EP 1 169 314 (and its divisional application EP 1 227 088), dealing with the crystalline base of citalopram and its use for purification. This patent was granted within 18 months despite the fact that the crystalline base was mentioned explicitly in prior art. Based on this patent the innovator initiated more than 30 court cases in 9 European countries. Several generic medicines companies faced interim injunctions, while others decided simply not to enter the market. It took four years after granting of the patent for EP 1 169 314 to be revoked on 20 July 2006 (and EP 1 227 088 on 25 October 2006).

Speeding up the EPO opposition proceedings would therefore be an effective and necessary means of preventing the assertion of ultimately invalid patents aimed at hindering competition from generic medicines. Of course, the delay would not be as problematic if the patent could not still be enforced in the courts during that opposition stage.

2. PATENT THICKETS AND FOLLOW-ON PATENTS

Patent quality is a direct reflection of the quality and scope of innovation that leads to a patent application. However, determining precisely what level of contribution to, or advance of, science and technology should be rewarded with the powerful right of monopoly is exceedingly complex. As the term of a patent is always the same, and the right given is always a monopoly, legislators and the examining bodies look to set a minimum standard of what deserves that level of protection, requiring that a patentable invention be both novel and inventive. Being vigilant in maintaining that standard for patents clearly poses an important challenge.

In the pharmaceutical sector this standard is often stretched, resulting in inappropriate patents that, based on strict adherence to the established criteria, should never have been granted. Due to a diminishing number of newly registered products and to contracting product pipelines, originator companies may be tempted to unjustly prolong the patent monopoly of existing products. The result is the 'evergreening' of a basic patent by means of secondary or follow-on patents designed to keep competitors off the market. These follow-on patents are often weak or trivial and, upon careful examination, it is clear that they should never have been granted. This is to a large extent due to a lowering of the patentability requirements, particularly the inventive step. A patent application presented in the right language and the right format may proceed to grant without the invention having made sufficient contribution to the state of the art to merit the grant of the patent. The following key areas of concern can be identified:

2.1. Unjustifiable extension of the monopoly on the drug by follow-on patents

In the pharmaceutical industry it has become common among patent holders of nearly all blockbuster drugs to attempt to extend the market monopoly beyond the length of time initially granted by the basic patent on the active substance. One of the strategies employed is the use of follow-on patents on non-essential features, a practice known as evergreening. Originators file numerous follow-on patent applications covering a drug in the hope that at least one of them will be granted and survive a litigation challenge. The consequence of this is often an extensive thicket or cloud of patents around a drug, the various parts of that cloud each typically falling into a number of different categories, namely:

a) the active pharmaceutical substance itself, typically the first patent(s) in the thicket. This may be a very specific claim to just one molecule, or the particular molecule might be disclosed only as part of a broader family;
b) a polymorph or hydrated form of the active substance;
c) a simple salt of the active pharmaceutical substance;
d) an isomeric form of the drug;
e) a substantially pure form of the drug;
f) an impurity inherent in an already disclosed process of making the drug;
g) formulations, whether in solution or in solid form;
h) concentrations in dosage forms; and/or
i) second medical use patents, particularly where that use is in a related field to the one originally disclosed in the first patent or a variation of the dosage regime already disclosed.

Categories b) through i) are often described as follow-on patents.

A good example of both an improperly granted follow-on patent and a patent thicket is found in relation to the product perindopril erbumine, discussed in Annex A.

Another striking example is the strategy to defend the originator's sales of Cipramil® (active ingredient citalopram hydrobromide), a drug for which patent protection was filed in 1976 and having an SPC expiry date in January 2002. Facing the looming expiry of the SPC, the originator filed approximately 30 patent applications between 1999 and 2002 covering the preparation and/or composition of citalopram. As already discussed above (1.4) the originator was successful in preventing generic competition on the basis of patents which were ultimately revoked.

Combination product patents are also problematic. After the first patent for a combination of an AII-receptor antagonist with hydrochlorothiazide (losartan/HCTZ) had been granted due to the surprisingly disproportional efficacy, it is difficult to understand how the efficacy of every following combination of any AII-receptor antagonist with HCTZ could also be considered surprising and therefore warrant the grant of a patent (eg, EP 733 366 B1, priority date January 7, 1988 for losartan/HCTZ and EP 753 301 B1, priority date June 7, 1993 for candesartan/HCTZ).

Patents to approved indications are also problematic. A good example of this is in the field of antidepressants, especially in selective serotonin reuptake inhibitors (SSRI's) in which the efficacy in treating depression is generally accompanied by positive effects in treating anxiety disorders and phobia, in particular a condition called Generalised Anxiety Disorder (GAD). GAD is an approved indication on two SSRI's products escitalopram and venlafaxine and which are patent protected in EP 0 639 374B (venlafaxine) which published in 1995 and also EP 1 200 081B (escitalopram) which published in 2002. It seems difficult to believe that it is inventive to discover that escitalopram has efficacy in treating GAD when it was known that SSRI's are effective in treating GAD. Even though the generics medicine may remove the indication of treating GAD from their product, and thereby avoid patent infringement, issues at a national level with achieving full generic substitution and full reimbursement remain and affect the commercial potential of the product.

Other examples are EP 1 121 375 (pure tibolone), the grant of which ignored well-known case law, EP 989 848 claiming an oval, coated tablet and EP 690 719 (the already discussed alendronate follow-on patent covering a dry mix composition of alendronic acid with lactose as diluent which is nothing more then basic pharmaceutical knowledge).

These follow-on patents stretch the limits of the patentability criteria and disrupt the delicate balance underlying the patent system. The European patent system should only award true inventions and should discourage patent applications for ordinary innovation. The overarching purpose of patents—ie, to support the creation and dissemination of products of new technology—should indeed not be lost sight of. In general, follow-on patents do not fulfil that purpose and clearly hinder competition from generic medicines.

It should be noted that this section should not be taken as a suggestion that all follow-on patents are necessarily invalid. They do, however, represent the types of patents that are most regularly and successfully challenged in examinations, in oppositions, and before national courts. But follow-on patents continue to be granted. This is to a large extent due to the structural deficiencies in the current examination system discussed above. Follow-on patents are even more difficult for a patent examiner to review properly for patentability, for the following reasons:

a. It is very difficult for examiners to raise *novelty* objections to follow-on patents. Unless the patentee of the original drug pre-published information about those incremental changes themselves, it is very unlikely that the examiners will be able to find any publications that clearly anticipate that particular polymorph/formulation/purity level as no one else will be looking at that drug yet in the light of the original basic patent on the active pharmaceutical substance. Even if third parties were working on the drug, many of these incremental changes would not be considered suitable material for publication, as they would not meet the editorial standard required of scientific or medical publications, ie, they must present some advance or further learning in the given area.

   A further difficulty for an examiner in reviewing these follow-on patents is that often the characteristics purported to have been 'invented' are inherent characteristics of the drug in question. As a mere discovery, they are clearly not patentable as they are not novel.

Examples of commonly patented developments which are inherent properties of a given drug are metabolites, isomers and polymorphs, particularly in polymorphic or crystalline forms of a given drug. The application of very standard experimental techniques to a drug will reveal its inherent properties. However, unless the patentee is required to provide more information to the EPO about how it came up with the invention (see above), the examiner is not in a position to determine the inherent properties of a drug.

b. Turning now to the question of *inventive step* in the pharmaceutical field, a great deal of drug development activity derives from widely used and generally understood methods and practices. These practices and the corresponding underlying knowledge will be referred to as the common general knowledge of a practitioner in the pharmaceutical industry. The inventive step criteria requires that an invention must not be obvious in light of the prior art. The inventive step requirement attempts to prevent awarding a monopoly to small changes to existing inventions. This is an area where examiners are not well equipped to assess the 'non-obviousness' of a product as, while they are always technically qualified, they do not generally possess the relevant common general knowledge nor practical experience. Nor do they take full advantage of the resources available to them, such as third-party observations and disclosure statements from the patentees, to assist them in understanding what the common general knowledge is. Examiners would therefore benefit from additional practical experience, and should further be required to lend more credit to third-party observations (as discussed above). Furthermore, a number of examiners are quite capable of making a proper assessment of the inventive step, but do not possess the necessary confidence to reject a patent application on the basis of lack of inventive step.

> This was clearly illustrated in the UK appeal proceedings in the perindopril litigation (see Annex A2). The product patent with respect to the α form of the tert-butylamine salt of perindopril (EP 1 296 947) was revoked in the first instance proceedings for lack of novelty and obviousness. EP 1 296 947 claimed the natural and inevitable product of the process that was the subject of the original basic patent. This has been confirmed in appeal, with the following striking comment: "The upshot of all this is that were the patent valid, Servier's monopoly in practice would last until 2020. But, as the Judge held and we confirm, it is invalid. And very plainly so. It is the sort of patent which can give the patent system a bad name. I am not sure that much could have been done about this at the examination stage. There are other sorts of cases where the Patent Office examination is seen to be too lenient. But this is not one of them. For simply comparing the cited prior art ('341) with the patent would not reveal lack of novelty and probably not obviousness. You need the technical input of experts both in the kind of chemistry involved and in powder X-ray diffraction and some experimental evidence in order to see just how specious the application for the patent was. The only solution to this type of undesirable patent is a rapid and efficient method for obtaining its revocation. Then it can be got rid of before it does too much harm to the public interest".

Hence, the problem with follow-on patents is closely interrelated with the previously discussed issues of quality as determining the presence of novelty or inventive step is a matter of judgment by the examiners. As mentioned, an important way of reducing the incidence of poor follow-on patents is for the EPO to continue to improve the quality of the examiners and their training, and to increase the number of more experienced senior examiners. These measures would inevitably lead to a more stringent application of the patentability requirements.

2.2. Multiple divisional patent applications which are entirely identical to the parent

A patent has significant impact on the development of a generic medicine even before it is granted, since a pending patent application poses a constant risk to a generic medicines company that the patent application will grant at any time. It is costly to prove that a patent is not valid,

and so generics companies will often decline to enter the market rather than invest the money to prove invalidity and clear the way for generic competition. A common way of maintaining the uncertainty generated by patent applications is to keep a series of pending divisional applications on file. Even if a generic medicines company is successful in defeating a parent application before the patent office or a national court, the generics company is still at risk that a patent covering substantially the same subject matter may issue from a pending divisional application in the same family which may be asserted against them.

A striking example of this conduct (and of evergreening in general) is the alendronate saga (Fosamax®). The basic patent on the active substance alendronate has been invalidated in most European jurisdictions. After a negative UK judgment, several claims of another patent (EP 402 152) were voluntarily abandoned in various countries. There was, however, another patent family related to the use of alendronate for the treatment of the bone disease osteoporosis according to a certain dosage regime. The mother patent, EP 998 292, was both successfully opposed before the EPO and revoked in a number of European jurisdictions. However, the patentee filed four substantially identical divisional applications, including EP 1 175 904 (for a 70mg once weekly dosage regime). EP 1 175 904 was granted and enforced to prevent the commercialisation of generic alendronate 70 mg (despite the revocation of the mother patent and 17 pending oppositions before the EPO against the divisional patent). Recently, the Dutch and Belgian courts came to the conclusion that EP 1 175 904 is invalid. The risk remains, however, that new litigation will be initiated if one of the other divisional applications is granted. It should be noted that in the meantime the originator has used its marketing resources to shift the market from Fosamax® to Fosavance®, which is the same medicine as Fosamax® with the addition of a small amount of vitamin D. This 'new' medicine, with no substantial added therapeutic value, is even the subject of a patent application despite the fact that patients who were prescribed Fosamax® in the past were instructed to consume this medicine in combination with vitamin D.

There are other examples where divisional applications might again become a problem, including simbicort (EP 613 371 B1 was revoked in October 2007 but divisional EP 1 101 493, covering the same subject-matter, is still under examination) and esomeprazole (magnesium salt patent EP 652 872 B1 was revoked but the patentee is continuing with divisional EP 1 020 461 for the same salt).

A simple way of preventing this strategy is to reject outright all divisional applications that exactly duplicate or do not vary significantly from the claims of the parent patent. This problem of so-called double patenting is prohibited (see C-IV, 6.4 of the EPO Guidelines for Examination). Nevertheless, (almost) identical divisional applications are still applied for and granted.

2.3. Specifying pharmacokinetic data without expressly linking it to a specific formulation

Another common follow-on patent strategy is to claim a pharmacokinetic effect of administering a particular drug, such as plasma levels of either the drug or metabolites, without linking it directly to the formulation used to achieve that effect. This is obviously problematic from a patent perspective: these types of patents claim a result without providing the method of achieving that result, for which many ways may exist.

One example of this is EP 758 244 B1, which claims the blood levels achieved by a new one-a-day dosing product of azithromycin (Zmax™). Therefore, the patent claim covers the desired result of the product without any limitation on how it is achieved, and thus effectively no generic medicines company can develop a bioequivalent product without infringing this patent. Azithromycin dosed at three times a day was already known and sold at the time of filing this application.

Unless there is something inventive in the selection of a particular pharmacokinetic effect which is fully supported by the patent specification, such patents must be limited to a specific formulation embodiment. If this is not the case, a generic competitor will not be able to come to market even if a new formulation is created which is entirely different to that used by the patentee, but which achieves that same pharmacokinetic effect. With these types of patents, generic medicines companies cannot develop and launch rival formulations without infringing the claims of the formulation patent even if entirely different excipients and formulating strategies are used.

2.4. Second and subsequent medical use claims

Based on grounds of public policy, namely that patents should not interfere with the freedom of medical practitioners to treat patients, limitations have been placed on the type of claims that can be granted for pharmaceuticals. The European Patent Convention (EPC) therefore deems claims directed to methods for medical treatment to be excluded from patentability. However, the first medical use of a known chemical compound is patentable despite this exclusion.

Many pharmacologically active chemical compounds are discovered to have different therapeutic effects and to have a second and subsequent medical use. Notwithstanding the fact that the EPC only permits first medical use claims, creative patent drafting has resulted in the patentability of second and subsequent medical use claims (by way of so-called 'manufacturing use' or 'Swiss type' claims). The EPO has allowed claims directed to the use of a known substance or composition in the manufacture of a medicament for a specified new and inventive therapeutic application. These Swiss-type claims must be limited to a therapeutic application which is new and inventive. The novelty must reside in the new second or subsequent therapeutic use.

In practice, however, the boundaries of Swiss-type claims have been stretched as patents are granted to protect discoveries relating to matters other than new indications, such as different dosage regimes, new patient populations, etc. Such patents are regularly improperly allowed by the EPO and arguably should not be permitted.

For example, several patents are currently in force claiming treatment of (different) diseases with the same compound by applying different doses of the drug. However, dose finding/ranging studies form part of the basic work performed during drug development. In most cases, all the indications are based on the long-known pharmacodynamic properties of the compound, ie, the inhibition of enzymes, blocking of ion channels, etc. They are not the result of inventive, but of routine, work. Examples here are the alendronate 70mg dosage regime patent or finasteride 5mg for the treatment of benign prostate hyperplasia and 1mg for the treatment of male pattern baldness. The patent for the latter indication (EP 724 444) extends the patent protection on the commercial product by more than seven years.

The possibility of second medical use claims often leads to unjustified monopoly rights and legal uncertainty, especially as the EPO and national courts have divergent views as to the scope of such claims. An updated version of the EPC, known as EPC 2000, came into force in December 2007. EPC 2000 contains a simplification of the form in which medical use claims can be drafted and should eliminate much legal uncertainty. The extent to which the EPC 2000 will succeed in resolving the issues surrounding the scope of second medical use claims remains, however, to be seen.

2.5. Genuine incremental innovation compared to simple changes in chemistry/formulation

It is not disputed that innovation often occurs in increments, nor that some of those increments are patentable. However, it is suggested that legislators and examining bodies need to look more carefully at the patent applications that are directed to those incremental inventions, and to apply patentability standards rigorously to ensure that the technological advance promised and the innovation encompassed in the patent application warrant the granting of monopoly rights. There are numerous examples in the context of pharmaceutical patents of incremental changes that are found by simply applying the common methods and standards of the pharmaceutical industry. Such incremental changes are not worthy of the market monopoly granted by a patent.

3. PATENT LITIGATION PROCEDURES OPEN TO ABUSE BY PATENTEES

Once a patent is granted, it is most valuable to a patentee when the rights conferred by it are exercised through litigation in each market and the monopoly rights are enforced. There is nothing inherently wrong with exercising patent rights, but in certain circumstances this might result in abusive and anticompetitive behaviour. It is clearly proper that a right holder has the opportunity to exercise his rights in court and to try to enforce them against a party believed to be infringing upon those rights. However, a patentee should want to resolve the issues at the earliest possible opportunity after becoming aware that an issue exists, and should not be permitted to delay. Situations where the right holder makes no effort to resolve the dispute because the *status quo* is favourable to him and deliberately misrepresents a situation purely for commercial gain clearly constitute an abuse of the judicial system.

Not only the behaviour of the patentee, but also the litigation framework itself, often creates problems and disadvantages for generic medicines companies. In general, the types of conduct and structural problems regarding patent litigation can be identified as follows.

3.1. The complexity and unpredictability of litigation across the European Union

The underlying structure of the EPC only provides for a common and single European patent application and granting system by the EPO. Once granted, a European patent is not a unitary patent, but is essentially a bundle of national patents. As a result, questions of patent infringement and validity are governed by various national laws and dealt with by the national courts under different procedural rules. There are no provisions in the EPC for a court with powers to settle patent disputes at European level. This purely national litigation system results in multiple patent suits involving high costs and complexity, forum shopping and uncertainty. As significant differences exist between the various national court systems and the way the courts handle patent cases, diverging and even contradictory decisions on the substance of the cases are frequent. Many of these courts are not even equipped to hear patent cases due to a lack of training and experience. Furthermore, many countries, such as Spain and Italy, have no institutionalised system in place to publish the decisions in patent cases. As a consequence, it is impossible for a body of law to develop adequately with an appropriate level of standards. In addition, the application of the law varies widely depending on the specific judge dealing with the case. Publication of all decisions would vastly improve the quality and predictability of patent litigation in those markets.

The recent introduction into EU legislation of Directive 2004/48/EC of the European Parliament and of the Council of 29 April 2004 on the enforcement of intellectual property rights (the 'IP Enforcement Directive') aims to harmonise the various legislative systems so as to ensure a high, equivalent and homogeneous level of protection of intellectual property rights in the internal market. The IP Enforcement Directive is designed to address the disparities in the means of enforcing intellectual property rights. This includes the arrangements for applying provisional measures (used in particular for the preservation of evidence), the calculation of damages, or the conditions for applying interim injunctions which have, until entry into force of the IP Enforcement Directive, varied widely from one Member State to another.

The IP Enforcement Directive, however, does not create a central judiciary composed of experienced judges properly equipped to deal with questions of validity and infringement on a pan-European basis. Patent enforcement remains a matter of national law and national courts. It is therefore very difficult for a generics company to develop a European launch strategy. The only

remaining option is very often to litigate on the same patent(s) and the same issues in numerous countries, with no confidence that the same decision will be reached in each jurisdiction.

A generic medicines company concerned that a given patent may be enforced against it fundamentally has three strategic choices for each and every country where a launch is contemplated.

1) *Launch at risk, awaiting and defending against any litigation the patentee may bring.* This can be expensive, to the point where it may exceed the value of the product launch. It is also always uncertain and unpredictable if the patent will be enforced or not. There is also a risk of (*ex parte*) injunction orders preventing the launch or resulting in a market recall.

2) *Seek to invalidate the patent prior to launch*, which is particularly important when the generic company indeed believes the patent is invalid, but will nevertheless be enforced. Invalidity proceedings should be prepared and initiated well in advance to allow a timely decision prior to launch. In many jurisdictions such pre-emptive invalidity action will not necessarily prevent a patentee from obtaining an interim injunction.

3) *Seek a declaration of non-infringement* where the court decides that a product does not infringe a right. Typically this involves, as a mandatory first step, informing the patentee of the nature of the product to be commercialised, with varying degrees of formal process required. The patentee will often request a number of 'clarifications', 'extensions of time', etc, which result in delays to this process. Again, in many jurisdictions such pre-emptive non-infringement action will not necessarily prevent a patentee from obtaining an interim injunction.

This process appears to be logical and simple, but this is only the case when there is no more than one patent on the product. This is not the situation where numerous follow-on patents exist. There are very few pharmaceutical products covered by a single patent on the product. A generics company may have to work through literally hundreds of patents and patent applications from the originator and other companies who are developing forms of that product, steering a precarious course through all of the potential issues. Multiplying the number of patents by the number of countries in which they can be enforced provides astonishing numbers and gives a clear indication of the extremely complex 'minefield' in which generic medicines companies are operating.

The lack of a central judiciary composed of experienced patent judges is regarded as one of the major deficiencies in the current patent system. The ideal—and most cost effective—solution would be to create a central European patent court to deal with questions of validity and infringement at a pan-European level. The European Commission has contemplated such an approach in its proposal for a Community Patent. The Community patent would be a single, unitary patent effective in all EU Member States. It would be litigated on a unitary basis in a specially created Community Patent Court within the framework of the European Court of Justice. Its decisions on infringement and validity would have effect throughout the EU. It is, however, questionable whether a political consensus can be reached regarding the Community patent.

The proposed European Patent Litigation Agreement (EPLA) represented an alternative litigation system for dealing with jurisdictional problems. Envisaged at the Intergovernmental Conference in Paris in 1999, the EPLA proposed an optional litigation system for the Contracting States Party to the EPC. The EPLA would have set up a European Patent Court as an independent body from

the EPO with jurisdiction over the validity and infringement of European patents. However, the EPLA proposal ran up against insurmountable institutional hurdles and has been abandoned.

That said, the European Commission is still seeking a compromise and a consensus on a single patent litigation system in Europe, recognising the inherent benefits in what was proposed under the EPLA. In April 2007 the European Commission published a Communication combining elements of the EPLA and a Community Patent Court by creating a unified litigation area on European patents and future Community patents. Whatever the outcome regarding the jurisdictional arrangements may be, it is clear that the current patent litigation framework needs improvement. An effective patent litigation system is essential for stimulating growth, innovation and competitiveness in knowledge-based economies.

3.2. Improper granting of interim injunctions

The IP Enforcement Directive requires European Member States to ensure that the judicial authorities can issue against an alleged infringer an interim injunction intended to prevent any imminent infringement of an intellectual property right or to forbid, on a provisional basis and subject, where appropriate, to a recurring penalty payment, the continuation of the alleged infringements of that right, or to make such continuation subject to the lodging of guarantees intended to ensure the compensation of the right holder. It is indeed essential to provide for interim injunctions for the immediate termination of infringements without having to wait for a decision on the merits of the case. Such measures are particularly justified where any delay would cause irreparable harm to the holder of an intellectual property right. It is, however, of the utmost importance that rights of the defence are observed, the proportionality of the interim injunction is ensured, and that the injunction is appropriate to the characteristics of the case in question.

As mentioned above, the IP Enforcement Directive has created a certain level of harmonisation, but interim injunctions are still a matter of national law. In consequence, varying standards are applied by national courts, leading to divergent decisions. This results in generic medicines companies being on the market with a product in some countries because interim measures on the basis of a patent are not possible or have been denied, while the same company is enjoined in other countries on the basis of the same patent.

Interim injunctions are very often inappropriate in patent disputes between originators and generics companies, and should be granted only as exceptional remedies.

1) It has been seen that national courts quickly feel uncomfortable in interim injunction proceedings, meaning that decisions which uphold the *status quo* are more than likely, ie, interim injunctions are easily awarded in certain countries. This is often due to the fact that the courts in injunction proceedings cannot make a full legal analysis of the parties' (patent) rights and can only make a *prima facie* assessment of the rights involved. In interim injunction proceedings courts are not even always fully informed about the parties' rights and their argument. A good example is the gemcitabine case in both the Czech Republic and Denmark discussed in Annex B. A party seeking preliminary relief that is seeking a decision from the court should be under a duty of candour, as in the UK. This is a duty owed to the court to present evidence that is for and against a party's position.

2) In various countries European patents are deemed to be *prima facie* valid, sometimes even when opposition proceedings are pending before the EPO and even when foreign

decisions exist that revoke parallel national patents stemming from the same European bundle patent. This is not surprising as many of the judges are not technically qualified to decide questions of infringement and/or validity on the face of the issue, and do not have the benefit of a court-appointed technical expert as would be the case in full proceedings on the merits.

3) Proceedings on the merits can be very time consuming in certain countries due to the backlog of court cases, a lack of experience, the appointment of technical experts, etc. If in the meantime a generics company is faced with an interim injunction order, the launch of generic competition can be delayed for many years. In extreme cases *ex parte* interim injunctions have been in place against generic medicines companies for nearly 12 months without being reviewed in appeal proceedings and without any progress in the proceedings on the merits. A good example of this is the venlafaxine XL case in Spain discussed in Annex E.

4) It is often argued that a patented invention must be protected due to the considerable investment made in research and development. The underlying idea is that patentees should in principle be entitled to profit from their investments. However, these considerations should not be of any relevance when the originator is enforcing follow-on patents after expiry of the basic patent as the originator company will have already recouped its R&D costs under the basic patent/SPC. In such circumstances the balance of convenience lies in not granting an interim injunction.

5) As mentioned above, interim injunctions are justified where any delay would cause irreparable harm. The harm for an originator does not seem to be irreparable. The harm is quantifiable and can be compensated with damages. There can be little argument that the benefit derived from a patent by the patentee (from sales at an increased price) is greater than the loss suffered by a generic medicines company seeking to enter the market (and who will enter the market with a substantially reduced price for the product in question and will always be sharing the market). As a consequence, commercial issues, rather than the merit of the patent infringement case, often drive the litigation strategy. Due to the substantial delays and expenses in determining patent issues in proceedings on the merits, the question whether or not there has been an act of patent infringement is ultimately of little significance. Often, the granting of an interim injunction will determine the issue and should be taken into consideration when making a judgment on the proportionality of the requested interim measures.

The negative financial consequences for the national health authorities resulting from a lack of generic competition should be a routine consideration in the search for the balance of convenience. The National Health Service (NHS), for example, was joined as a party to the interim injunction proceedings in the clarithromycin case (Generics/Ranbaxy/APS v Abbott Laboratories (2004)) in the UK. Had an interim injunction been granted, the patentee would have been required to give a cross undertaking to the NHS as damages. There is no doubt that the significant value of the payout to the NHS that would have been required would in future encourage a patentee to only seek an interim injunction when it was genuinely believed that the patent in question was both valid and infringed. This fact should serve to encourage national health care authorities to become involved in interim injunction proceedings, not only to ensure that they are compensated should an interim injunction be improperly granted, but also to dissuade patentees from seeking interim injunctions in all but the clearest of infringement cases.

In conclusion, the standard for obtaining an interim injunction should be returned to its roots as an equitable remedy. This means that a litigant should be required to establish irreparable harm that cannot be compensated by monetary damages before a court takes the far-reaching step of enjoining a product. Applying this standard would serve the dual goal of encouraging patent owners to commercially develop or license their innovations, and of ensuring that injunctions are not used simply as a tactic in litigation, which is essentially the reality today.

3.3. Other patent litigation issues

Once a generic medicines company has made a strategic choice in relation to each element of the patent thicket surrounding a pharmaceutical product, significant difficulties in implementing that strategy still remain.

- **The length of the proceedings on the merits (non-infringement and/or invalidity proceedings)**

  As mentioned above, invalidity proceedings and/or non-infringement proceedings on the merits often take a great deal of time for a variety of reasons. At the same time, it is in the patentee's interest to keep the generics company in a state of uncertainty about whether their product infringes a patent or not for as long as possible. The patentee often does so by drawing out the process through such tactics as taking advantage of the formalities of the document service process, requiring all points to be proven beyond reasonable limits, and demanding the disclosure of commercially sensitive information, etc. In the meantime, competition from the generic medicine is prevented if an interim injunction is granted during the proceedings.

- **Split infringement and invalidity courts**

  A bifurcated patent litigation system exists in certain countries (Germany, Hungary, Czech Republic and Poland), meaning that issues of infringement and validity are decided by separate courts. Invalidity may not be raised as a defence in an infringement action (unless there is a clear cut attack based on novelty). In practice, invalidity actions take longer than infringement proceedings. In Germany, nullity proceedings cannot be started before the Federal Patent Court until the EPO opposition proceedings have been concluded or the opposition period has expired. If a generics company has no non-infringement arguments but does have strong invalidity arguments, there is a risk that the generic medicines company will be prevented from launching or will be required to recall its product from the market pending the outcome of the invalidity proceedings.

  Another difficulty is that patentees often take mutually exclusive positions in the various proceedings, for example with respect to the scope of the patent claims. In invalidity proceedings, it is often important to argue a narrow scope for a patent claim in order to avoid issues of validity caused by prior art that is similar to the patent claim. In infringement proceedings, however, the patentee will often argue a broader interpretation of the claim to encompass as many infringing acts as possible. In a bifurcated system generics companies lose the possibility of deploying 'squeeze' arguments to prevent a patentee from giving a different interpretation to the same patent claim.

- **Inability to disclose information on a confidential basis**

  As discussed above, a patentee is entitled to defend its patent rights. A common strategy for a generics company to ensure that the originator will not take action under a patent

upon launch of the generic product is to clear the way by seeking a declaration of non-infringement. In order to obtain such a declaration many EU Member States require the non-confidential disclosure of information about the generic product to both the originator and the court. However, many generic medicines companies are understandably reluctant to provide such information in a non-confidential way for fear it could be used against them in another context, for example, in relation to the regulatory approval process.

- **Which of the many patents should be nullified?**

  Any one of the patents owned by the right holder that is marketing a pharmaceutical may be exercised against a generic medicines company in order to seek preliminary relief. It is neither possible nor commercially feasible to attack all of them. Deciding on a strategy to employ for launching a product upon expiry of the active substance patent is the subject of very careful consideration. A good example of this is perindopril (see Annex A1). When the active substance patent expired in Western Europe, there were at least 38 other granted patents, including 4 to polymorphic forms and a further 30 to processes used in producing perindopril. Generics companies need to look at the cost and time required to obtain a decision in relation to each one of those patents. For national proceedings in Germany, it costs at least €75,000 to start a nullity proceeding. It will then take nearly two years for a decision to be handed down. In the UK, a bare minimum of €150,000 is required to resolve a very simple patent nullity action, but a full hearing on non-infringement could cost as much as €500,000 for a single patent. A full hearing on both infringement and invalidity can be expected to cost significantly more than in any other country. NO generic company can afford to take on such costs for every poor quality patent that forms part of a patent thicket.

- **Local forum shopping**

  Many countries, such as Germany, Austria, Switzerland and Italy, operate numerous regional courts that maintain equal jurisdiction over patent matters. This obviously leads to forum shopping and the possibility of inconsistent decision making.

  In Italy, the patentee of the patent IT 1 201 087 (equivalent national patents had been revoked in UK, DE and USA) initiated infringement proceedings before three separate regional courts (Milan, Genoa and Florence) against the parties that introduced a generic version of alendronate in Italy, their suppliers and pharmacy associations. Eventually, this resulted in two generics companies remaining on the market following a decision from the court in Milan, which refused to grant an interim injunction, and one party being enjoined (Teva) following a decision from the district court of Genoa on appeal. Factually, all companies were selling products which, for the purposes of the issue at hand, were identical. More information is provided in Annex D.

  This was also the case in the Belgian alendronate litigation where several generic medicines companies were sued by MSD with respect to alendronate. In order to prevent the launch of generic alendronate, MSD undertook summary proceedings against these competitors on the basis of SPC Nr. 96C0027. Differing judgments were handed down by various courts. The Brussels Court of Appeal issued injunction orders against three generics companies. The Brussels Court of Appeal did not take into account the invalidity arguments raised by the generics companies, nor the various foreign judgments invalidating equivalent national patent rights. The Court of Appeal of Brussels decided that the validity of a patent cannot be assessed in summary proceedings and deemed the SPC to be *prima facie* valid without any examination of the invalidity arguments. The Court of Appeal of Antwerp, however, came to the opposite conclusion in the summary proceedings against a different generic medicines company. The Court regarded the SPC to be *prima facie* invalid, *inter alia* in light of the foreign judgements. This is, however, exceptional. Belgian courts do not tend to take foreign judgements into consideration when assessing the *prima facie* validity of the patent rights invoked.

  A reduction in the number of regional courts, ideally to one court per country, would allow expertise to be quickly established and would eliminate the possibility of the situation described above from occurring again.

4. OTHER PATENT-RELATED BARRIERS

The following points present various other problems in the pharmaceutical market related to patents which should be addressed, but which do not fit comfortably in the categories above.

4.1. Patent linkage

Patent linkage is the practice of linking either market approval, the pricing and reimbursement status or any regulatory approval for a generic medicine to the patent status of the originator reference product. Hence, patent linkage is an administrative and/or regulatory scheme under which a regulatory and/or other responsible agency in a country will not grant the relevant authorisation for a generic medicine to any party not authorised by the patent holder for that drug product until either (a) the expiry of all relevant patents covering the drug product, or (b) the determination by a governmental body, either executive or judicial, that the relevant patents are not being infringed, or are invalid or unenforceable.

Patent linkage is not part of EU pharmaceutical legislation and should be avoided for the following reasons:

1) Regulatory offices are not in a position to make an informed decision about the applicability of a patent to a particular generic product, and so should leave that issue to the courts. Nor can they in any way be held liable if they approve a product that is covered by a patent so there is no need for them to be involved with the question of patents. Originators try to force patent linkage upon regulatory authorities through tactics such as sending warning letters accusing them of patent infringement when they accept or approve marketing authorisations and/or applications for price and reimbursement status. In 2007 originators started 70 court cases in Portugal against the regulatory authorities. Creating formal patent linkages will only encourage such practices.

2) Some patent linkage schemes are inconsistent with the *Bolar*-exception which was recently introduced by Directive 2004/27/EC amending Directive 2001/83/EC on the EU code relating to medicinal products for human use. This exception provides the manufacturers of generic medicines an exemption for pre-market testing: *"Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."*

3) The scope of the exemption, however, remains unclear due to the use of ambiguous, vague and broad terminology. This is complicated by a diverging implementation in the various EU Member States. The term 'consequential practical requirement is particularly nebulous and will inevitably lead to disputes. One important question is whether filing an application for a price and reimbursement decision falls within the scope and intention of the Bolar-exception. This is very important for the patent linkage discussion: if the Bolar-exception applies to such applications, the regulatory authorities cannot make their decisions depend on the patent status of the reference product. It is crucial for the generic medicines industry that pricing and reimbursement issues fall within the scope of the Bolar-exception, as was recently decided in the Belgian alendronate litigation (2007).

   Reference can also be made to the 2005 decision of the Swedish Medical Products Agency in which it was decided that the generic pharmaceutical risperidone was interchangeable with the patented pharmaceutical Risperdal. In appeal it was argued that the Medical Products Agency did not have the right to decide on the interchangeability of pharmaceuticals that were still protected by patent. It was even argued that the decision of the Medical Products Agency constituted contributory patent infringement. In its judgment

delivered in February 2007, the County Administrative Court rejected the appeal. It was, *inter alia*, decided that the Medical Products Agency cannot take a position on issues regarding intellectual property rights, but can only decide whether or not the medical demands for interchangeability have been met.

4) Patent linkage is inconsistent with the concept of the application of patent rights. Neither the granting of a market authorisation nor obtaining price or reimbursement status can be seen as the actual commercialisation of the product. These are simply administrative procedures required for placing the product on the market once the patent has expired.

Despite these points, certain countries in Europe have already implemented forms of patent linkage schemes along the lines just described. Hungary, for example, imposes a requirement on generics companies to make a statement about the patent status as part of a regulatory dossier submission and will not approve a generics submission without it. Slovakia, in its original implementing legislation of the EU pharmaceutical legislation, stated that the regulatory authorities could even reject outright the application for the registration of a generic medicine if the reference product or active substance used in the reference product was protected by a patent/SPC. Although this provision has been dropped following intervention by the European Commission, the law still contains patent linkage in that the market authorisation given to a generic medicine will be suspended until patent expiry. The European Commission is now investigating this provision.

4.2. Statements to authorities

Patents can also play a (indirect) role in tendering processes. A large range of pharmaceutical products are sold via tenders. A common tactic during the tendering process is for an originator company to make broad statements about the patents protecting their product and their relevance to other products competing in the tender. While it is important for a tendering authority to make sure it finds a product that can guarantee continuous supply, they should not be influenced by any statements with regard to the patent landscape.

4.3. Shifting consumer demand with marketing campaigns

When a product is reaching the end of its original patent life, an originator will typically release a new form of the product, such as a new salt, tablet or extended release preparation, that is often covered by a 'follow-on' or second medical use patent with a late expiry date. These 'new' products often have the advantage that the toxicological and safety profiles of the basic compound have been well established which assists in obtaining the necessary regulatory approval for them. Extensive marketing efforts are then focussed on shifting consumer demand from the old product (covered by the original, soon-to-expire patent) to the new product covered by the newly 'refreshed' patent, hampering competition with the original product from generic formulations. The shift discussed above from Fosamax® to Fosavance®, which is the same medicine as Fosamax® but with the addition of a small amount of vitamin D, is a striking example of this strategy. A further example is presented in Annex A2.

4.4. SPC granted on the basis of incorrect information

In the pharmaceutical sector extensive research and testing is necessary and regulatory approval is required before a medicine can be placed on the market. To compensate for the long period of time needed to obtain such regulatory approval, Supplementary Protection Certificates (SPC) have been introduced. An SPC comes into force only after the corresponding patent expires. The

term of an SPC depends on the date of issuance of the first market authorisation within the EEA and has a maximum life time of five years. Applications for an SPC must be filed on a country-by-country basis. There is no unitary European SPC, only national rights.

National patent offices rely on information provided by originators to determine the first market authorisation within the EEA. This creates scope for originators to distort the system by providing false or misleading information.

> One obvious example of such behaviour is that of AstraZeneca in relation to its omeprazole product, which resulted in the European Commission finding AstraZeneca guilty of abuse of dominant position contrary to Article 82 of the EC Treaty and imposing a fine of €56 million. In this case, in applications to 10 different national patent offices AstraZeneca failed to mention the date of the earliest market authorisation in the EEA (ie, France) and instead supplied information (which was itself misleading) as to the date of the market authorisation in Luxembourg. As a result, AstraZeneca obtained SPCs to which it was not entitled in Germany, Norway and Finland, and obtained SPCs for a period longer than it was entitled to in a number of other Member States.

To help prevent this type of misconduct, patent offices should be encouraged to either require patentees to provide concrete evidence of the first marketing authorisation of the active substance in the European Union, or to seek independent proof of the earliest approval date. At present, many countries simply require a patentee or their agent to fill in a form stating the earliest approval date without providing further evidence. In contrast, the US Patent Office works directly with the Federal Drug Administration to obtain relevant approval dates when making similar assessments. There is evidence that national patent offices already feel comfortable taking similar steps; for example, AstraZeneca failed to obtain an SPC for a period longer than it was entitled to in the UK because the UK Patent Office pursued the issue of the date of the first market authorisation independently rather than simply relying on the information provided by AstraZeneca.

Furthermore, patent offices should require the patentee (not the patentee's local agents) to provide a formal, sworn declaration to the effect that the date provided is indeed the earliest approval of the relevant active ingredient in the European Union. This would constitute a strong disincentive against providing inaccurate or misleading information and would improve the quality and accuracy of future SPCs.

IV. RECOMMENDATIONS

To overcome the problems outlined above, we suggest the following modifications to the current legal and regulatory environment related to pharmaceutical patents.

1. To improve patent quality:
    a. provide adequate resources and continue to encourage the EPO to improve the quality of patents that are granted by applying a consistently high standard of thoroughness in patent examination by well-trained examiners;
    b. remove the requirement for EPO examiners to be fluent in three languages in order to allow the selection of examiners from a larger, more technically skilled pool of candidates;
    c. require patentees to file high quality applications and introduce the duty of candour to ensure that all information relevant to the patent being examined by the EPO is disclosed by the applicant;
    d. introduce a mechanism (prosecution history estoppel) whereby patentees are held accountable for statements made during prosecution when a patent is being litigated;
    e. guarantee that interested parties have sufficient opportunity to alert the EPO about questionable patents within the EPO granting process itself; and
    f. accelerate the opposition procedure.
2. To prevent the creation of patent thickets and reduce the incidence of poor follow-on patents:
    a. improve the quality of patents as outlined above and apply a rigorous assessment of patentability requirements;
    b. prevent the filing of divisional patents that are essentially identical to the parent application;
    c. require that patent claims with respect to the pharmacokinetic effect of administering a particular drug be directly linked to the formulation used to achieve that effect;
    d. limit the scope of second and further medical use patents; and
    e. grant patents only to genuine incremental innovation and not to simple changes in chemistry or formulation.
3. To improve the patent litigation system in order to avoid excessive and abusive litigation and diverging and unbalanced decisions:
    a. create a national litigation framework with technically qualified and experienced patent judges who can reach a decision on the merits of a case within a reasonable period of time;
    b. publish all patent court decisions in an EU register to provide clarity and to increase harmonisation, and to assist in moving towards the creation of a common jurisprudence on European patents;
    c. reach a consensus on a central patent judiciary in Europe;

d. avoid interim injunctions by inexperienced judges without a proper assessment of the rights of all the various parties involved;

e. require common standards of evidence and a duty on all parties to the litigation to present evidence to the court both for and against awarding a preliminary injunction;

f. seek out a proper balance of convenience by the courts in which *inter alia* the patentee's evergreening strategy, the costs to national health care authorities, etc are taken into account;

g. involve the health care authorities in patent proceedings, particularly in applications for interim injunctions;

4. To overcome some of the other barriers to entry described above:

   a. reject all efforts to introduce patent linkage;

   b. prevent originators from obtaining patents for and switching the market to 'new' products that offer no substantial added therapeutic advantage over the previous product; and

   c. require patentees to provide sworn statements and supporting evidence for the date of first marketing authorisation in the EEA when applying for an SPC.

ANNEX A1 | Patent Thicket for Perindopril

Granted patents in the name or control of the originator, as of February 2008

1. EP 0 049 658 B — expired with SPC 21 June 2003 [UK date] — compound
2. EP 1 296 947 B — alpha polymorph of perindopril erbumine — revoked in UK
3. EP 1 294 689 B — beta polymorph of perindopril erbumine
4. EP 1 296 948 B — gamma polymorph or perindopril erbumine
5. EP 1 354 873 B — arginine salt of perindopril — launched in a number of CEE markets
6. EP 1 032 414 B — combination of perindopril and a diuretic (indapamide)
7. EP 1 467 750 B — orodispersible formulation of perindopril
8. EP 1 345 605 B — thermoformed CR formulation of perindopril
9. EP 0 308 340 B — process for preparing perindopril
10. EP 0 308 341 B — process for preparing perindopril
11. EP 1 367 063 B — process for preparing perindopril
12. EP 1 367 062 B — process for preparing perindopril
13. EP 1 422 236 B — process for preparing perindopril
14. EP 1 420 029 B — process for preparing perindopril
15. EP 1 420 028 B — process for preparing perindopril
16. EP 1 403 278 B — process for preparing perindopril
17. EP 1 403 277 B — process for preparing perindopril
18. EP 1 403 275 B — process for preparing perindopril
19. EP 1 400 531 B — process for preparing perindopril
20. EP 1 380 591 B — process for preparing perindopril
21. EP 1 380 590 B — process for preparing perindopril
22. EP 1 371 659 B — process for preparing perindopril
23. EP 1 362 864 B — process for preparing perindopril
24. EP 1 367 061 B — process for preparing perindopril
25. EP 1 354 876 B — process for preparing perindopril
26. EP 1 354 875 B — process for preparing perindopril
27. EP 1 354 874 B — process for preparing perindopril
28. EP 1 348 684 B — process for preparing perindopril
29. EP 1 338 591 B — process for preparing perindopril
30. EP 1 333 026 B — process for preparing perindopril
31. EP 1 323 729 B — process for preparing perindopril
32. EP 1 321 471 B — process for preparing perindopril
33. EP 1 319 668 B — process for preparing perindopril
34. EP 1 279 665 B — process for preparing perindopril
35. EP 1 256 590 B — process for preparing perindopril
36. EP 1 268 424 B — process for preparing perindopril
37. EP 1 272 454 B — process for preparing perindopril
38. EP 1 268 398 B — process for preparing perindopril

ANNEX A2 | Perindopril Erbumine

Servier have been granted patents covering the alpha, beta and gamma polymorphs of perindopril erbumine. The alpha form is the most thermodynamically stable form (EP 1296947). The '947 patent was opposed by a number of parties at the EPO.

A number of generic medicines companies sought to launch a product containing the alpha form of perindopril erbumine, including Apotex, Lupin, Teva, KRKA and Niche. The UK court granted preliminary injunctions against all generic companies.

Lupin settled and withdrew their opposition at the EPO as well as their action in the UK. In addition, Lupin assigned all their patent rights to Servier and received a cash payment of €20 million from Servier, as discussed in the following press release.

> MUMBAI (Thomson Financial) - India's Lupin Ltd said it has earned 20 mln euro by selling additional patent rights of its hypertension drug Perindopril to France-based Laboratoires Servier.
>
> 'This income significantly boosts our performance for the current year,' said Lupin managing director Kamal Sharma, in a filing to India's National Stock Exchange.
>
> In April this year, Servier had reportedly bought the process patents on the drug -- marketed in Europe as Coversyl -- for 20 mln eur, while Lupin retained other patent rights.

Krka settled and withdrew their opposition at the EPO as well as their UK action, and consented to the termination of the proceedings Servier had commenced against them in national proceedings for patent infringement in Hungary and Slovenia, their manufacturing site. In return, Krka were allowed by Servier to launch in the Central Eastern Europe region, in those countries where there is a patent equivalent to EP 1 296 947 B. Other generics companies now have approval of perindopril erbumine in the CEE, but have not launched. Servier have made it known locally that their rights in EP 1 296 947 B will be enforced vigorously despite being revoked in the UK. In these markets the originator has launched the arginine form of perindopril and is shifting its marketing efforts to promote this new patent protected form.

Apotex continued the case and the patent was revoked in the UK at the first instance. The basis for the revocation was that the alpha form was inherently disclosed in the example of the original compound patent EP 49 658.

Unusually, Servier made a pleading to the court that the preliminary injunction continue until the appeal was decided. This had the effect of delaying the publication of the decision to revoke the UK patent (on the basis that the position and *status quo* had to be preserved for both parties until the new motion had been heard). After a brief interim period where the first instance judge continued it until the motion for an appeal was heard by the appeal court, the motion was denied and the appeal was rejected. Generic perindopril was denied access to the UK market up until Q3 2007, some four years after the compound patent, including an SPC, had expired.

In addition to this strategy, Servier has a granted patent EP 1 354 873 B for perindopril arginine, another simple salt form. They have begun shifting consumers to the arginine form before generic companies can enter such markets as Eastern Europe and Australia. This different form of the drug has not shown any additional therapeutic benefit and in fact has caused significant confusion amongst doctors due to the different prescribing regime required by the new salt (8mg of perindopril erbumine is the dosing equivalent of 10mg of perindopril arginine as the arginine salt has a greater molecular weight; the amount of the active perindopril is the same). Servier

claims additional stability; given the worldwide launch of the erbumine form, this would seem to provide a relatively meaningless advantage to the patient.

Finally, Servier filed 29 process patents for ways of producing perindopril. By further taking assignment of Lupin's process patents they are attempting to create a vast patent thicket. Annex A1 lists the details of all of the patents that have been granted for perindopril.

ANNEX B | Gemcitabine—(Eli Lilly)

Czech Republic

Gemcitabine is an important product in the field of oncology. The patent that protects, or protected, gemcitabine *per se* across Europe has expired in the Czech Republic. Eli Lilly is the owner of a follow-on patent in the Czech Republic CZ 291165 B1 on an improvement to the process for preparing gemcitabine.

In October 2007, prior to the launch of its gemcitabine product in the Czech Republic, PLIVA informed Eli Lilly of its intent to launch and provided details of the route of synthesis used, including reasons why the '165 patent was not being infringed.

Nevertheless an *ex parte* preliminary injunction was sought by Eli Lilly and granted. In its application for the injunction Eli Lilly provided no direct evidence of any infringement of the patent by PLIVA's product. The only evidence submitted by Eli Lilly were theoretical propositions from 'experts' that the only economically viable route to make gemcitabine was by the one route protected by the patent. Facts and submissions made by PLIVA to Eli Lilly in advance of the hearing were apparently not put before the judge for consideration when making his decision on ordering a preliminary injunction.

A judge should never be allowed to issue an interim injunction in patent proceedings without hearing from both parties. In any event, a more experienced judge in patent matters would not be convinced by this type of 'negative proof' of the need to provide a remedy as draconian as an interim injunction on an *ex parte* basis.

Since then further submissions have been made to Eli Lilly confirming the facts disclosed in PLIVA's initial letter, including all of the relevant aspects of the manufacturing route submitted in confidence to the medicines agency. As of April 2008 the injunction remains in force and there are currently no generic competitors on the market.

The total sales of gemcitabine reached €5.9m in the Czech Republic in 2007 (IMS data)—solely by Eli Lilly.

Denmark

A similar situation arose in Denmark at the end of 2007 under the EP equivalent of patent CZ 291165. Despite Eli Lilly having access to detailed information regarding the actual process for manufacturing gemcitabine used by Mayne Pharma, it sought an interim injunction in Denmark against Mayne Pharma using the same negative proof as was used in the Czech Republic, ie, there was no commercially viable way to manufacture the drug other than the method under patent. Eli Lilly made this assertion despite the clear evidence on the record that this was not the case and despite having sufficient knowledge of the actual process Mayne Pharma was using. Instead of focussing on proving actual infringement, Eli Lilly relied on unsupported assertions that Mayne Pharma was doing something other than what it stated in the disclosed documents, which included excerpts from its regulatory submissions. In a similar situation a UK court stated that non-compliance with the process described in a regulatory dossier would be 'commercial suicide'. In March 2008 the Danish court issued an interim injunction against Mayne Pharma on the basis of this incomplete argument. Without intending disrespect to the Danish court, this case provides an example of a situation where the inexperience in dealing with the technical issues involved in patent matters can lead to an incorrect decision, creating an unjustifiable barrier to generic entry.

ANNEX C | Abbott vs Teva (The Netherlands)

The Enforcement Directive was implemented into the Dutch Code of Civil Procedure on 1 May 2007 by way of section 1019. As a result, new measures for the preservation of evidence became available.

On 10 May 2007 Abbott requested an *ex parte* seizure of documents for the purpose of safeguarding evidence, asserting there was imminent infringement of Abbott's patent rights. Preliminary relief judges in Utrecht and Haarlem granted this request *ex parte*, and from 10-15 May a search was conducted in the Teva offices in Utrecht and Haarlem, including a search of the server computers, which effectively extended the search beyond Europe.

Documents relating to the alleged infringement were seized and descriptions of the documents were made. The seized documents were remanded by court order to the custody of the Bailiff. Abbott filed a suit for preliminary relief to request that the seized documents be made available to them while Teva, in a counterclaim, asked for the seizure to be lifted.

The matter was heard in the District Court of The Hague by the preliminary relief judge on 28 June 2007 in one of the first such hearings in Europe. The Court found the seizure to be unlawful and that it should be lifted, holding that:

1) the initial application for preliminary relief and the seizure had been conducted in the name of the wrong Abbott entity;

2) the threshold for evidence required to instigate evidential seizure should be set lower than the likelihood of infringement in preliminary injunction proceedings (reasonably available evidence);

3) Abbott had not made out a plausible argument that a threat of infringement existed; and

4) Abbott had only submitted evidence that Teva had applied for marketing authorisations in various countries and was preparing the launch of a generic product without any evidence that the marketing authorisations would be used prior to expiry of any relevant Abbott patent.

Despite this ruling, the first instance judge allowed the seizure to proceed at great risk to Teva. This case highlights the risks to generics companies emanating from the new IP Enforcement Directive.

ANNEX D | Litigation on Alendronate in Italy

National infringement proceedings were brought in Italy under IT 1 201 087 by Istituto Gentili SpA, which belongs to the Merck group, against a number of generic medicines producers following approval in October 2006 of generic alendronic acid.

1) **The proceedings against ratiopharm GmbH and Pliva Pharma SpA.**
   In this case Istituto Gentili started its precautionary claims for a preliminary injunction before the Milan Court. A nullity action had been filed in July 2005 at the Milan Court by ratiopharm and Pliva. The precautionary infringement action had to be started before the Milan Court, which was handling the case on the merits, due to article 669 quarter of Italian Civil procedure;

2) **The proceedings against Arrow Generics UK—suppliers of product to parties in 1.**
   In this case Istituto Gentili presented the claims before the Court in Florence due to the fact that: (i) there was no pending proceedings between Arrow and Istituto Gentili in Italy and (ii) Arrow does not have any head-offices or legal representative in Italy; in this situation the petitioner may introduce the claims before the Court in whose jurisdiction the same petitioner has its head-offices;

3) **The proceedings against Arrow Generics UK and ratiopharm GmbH by Abiogen srl.**
   The latter is one of Istituto Gentili's co-marketers and as such is empowered to act against a potential infringer. Abiogen started both cases before the Florence Court for the same reasons mentioned in point 2);

4) **The proceedings started by Istituto Gentili against Teva Companies before the Genoa Court.**
   Istituto Gentili was able to take action before the Genoa Court due to the fact that a Genoa association of pharmacists issued an advertisement for the Teva product and Istituto Gentili involved this association in the proceedings in Genoa.

With regard to the outcome of the proceedings:

a) the preliminary injunction was rejected by the Milan Court on 1 March 2007 and no appeal was filed;

b) the precautionary claims were rejected by the Florence Court on 27-30 November 2006 and such rejection was confirmed after the appeal proceedings;

c) the claim for a preliminary injunction was waived by Abiogen srl at the hearing fixed to discuss the claim on 14 November 2006;

d) the preliminary injunction was rejected by the Genoa Court. Istituto Gentili filed an appeal and the panel of judges of the Genoa Court issued the requested injunction on 8 January 2008.

There are 12 courts in Italy where infringement proceedings may be started.

ANNEX E | Opportunistic Litigation

Venlafaxine XL (Wyeth)—Spain

Venlafaxine XL is the sustained release formulation of venlafaxine, which is used as an anti-depressant. The patent that protects venlafaxine as a molecule has now expired in Spain. As of the date of writing this report no generic venlafaxine xl product exists on the Spanish market despite several marketing authorisations being granted by the Spanish agency. Wyeth is the owner of patent ES 2 210 454 and ES 2 174 864.

Wyeth has successfully obtained a preliminary injunction against all marketing authorisation holders in Spain. Two injunctions in particular are in place that the author is aware of[1,2] (Qualitec[2] since May 2007 and Laboratorios Edigen[1] since June 2008). In these cases the patentee, Wyeth, and the local operating company were specifically informed of the nature of the product to be launched and were provided with clear evidence that the product did not infringe the patent.

The issues at stake here are simple. The right holder is aware that at least some of the products do not infringe its patents (as expressed in an open letter). In addition, identical products are on sale in other territories where equivalent rights exist with no enforcement, such as in Poland.

The patentee could easily ask for clarification or a submission of samples. All correspondence has been ignored.

The total sales of Venlafaxine XL amounted to €120m in Spain in 2007 (IMS data).

The following is a Summary as of April 2008:

Mercantile Court Nr. 2 of Madrid—Qualitec have been enjoined *ex parte*.

Mercantile Court Nr. 3 of Madrid—Laoratorios Edigen have been enjoined *ex parte* and proceedings against ratiopharm will be heard. This company is not currently enjoined, but has not yet launched its product.

Mercantile Court Nr. 4 of Madrid—the following companies have also been enjoined *ex parte*: Cinfa, Normon, Vegal, Toll Manufacturing Services, Winthrop, Farmalider, Rimafar, Dermogen Pharma, Belmac and Davur.

Patents play an important role in modern society. In order to encourage the creation, dissemination and efficient exploitation of technology, patents provide inventors with a limited term legal monopoly on their invention.

Generic medicines play an equally important role in promoting pharmaceutical innovation and ensuring the affordability and sustainability of European healthcare systems. In this regard, immediate market access of generic medicines after patent expiry is of crucial interest to society, and any hurdle to this access should be eliminated.

However, a number of developments point to a strategic use of patents—of sometimes questionable quality—which is directed more toward preventing others from innovating and competing, than toward creating truly innovative products. When misused in this manner, patents can present a barrier to entry onto the generic medicines market. This report identifies some of the hurdles that generic medicines companies face in this regard in the European Union.

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