



The ‘obvious to try’ method of addressing strategic patenting: How developing countries can utilise patent law to facilitate access to medicines*

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Introduction

The problem of access to affordable and effective medicines is currently considered to be of critical importance around the world. This issue affects both developing and developed countries, which have been increasingly suffering from high drug prices. It puts significant pressure on national healthcare budgets and forces governments to reconsider their policies in this field. While in the past, countries were free to develop their national IP-related policies to combat high prices and facilitate access to medicines in accordance with their local needs,¹ with the TRIPS Agreement coming into force, they must now operate within the limitations set by this international instrument. In particular, prior to TRIPS, many countries denied patent protection on medicines, or provided only limited protection to the process of their manufacture.² However, TRIPS, which came into force in 1995, established new international rules on patentable subject matter and provided that: ‘...patents shall be available for any inventions, whether products or processes, in all fields of technology...’.³ The consequence of this provision is that it obliges all Member States of the WTO to provide patent protection to all inventions, including pharmaceuticals. In other words, patent protection must now be available for medicines.

These changes have been particularly detrimental for developing countries that cannot afford the cost of expensive patent-protected medicines.⁴ The problem is further exacerbated by the imposition of additional restrictions in the field of pharmaceuticals on developing countries as a

result of bilateral trade pressures and trade agreements, many of which include the so-called ‘TRIPS-plus’ provisions.⁵ These provisions prevent developing countries from using TRIPS flexibilities and often exceed the obligations under the TRIPS Agreement.⁶ In addition to the high level of protection for medicines established by these international and bilateral instruments, pharmaceutical companies utilise various business strategies that allow them to further strengthen the protection of their products. Among such practices is strategic patenting, or ever-greening, which refers to a specific strategy under which ‘patent owners take undue advantage of the law and associated regulatory processes to extend their IP monopoly particularly over highly lucrative “blockbuster” drugs by filing disguised/artful patents on an already patent protected invention shortly before expiry of the “parent” patent’.⁷ Such strategies allow originators to secure the most efficient, broadest and longest possible patent protection for their successful products.⁸ As the European Commission noted in its Pharmaceutical Sector Inquiry Report,⁹ these patent strategies have the capacity ‘to extend the breadth and duration of [the originators’] patent protection’¹⁰ and ‘to delay or block the market entry of generic medicine’.¹¹

In these complex and highly restrictive conditions, developing countries are in a difficult position: on the one hand, they are required to meet their obligations under international and bilateral agreements, while, on the other hand, they are desperate to provide their citizens with essential, often life-saving medicines. The latter forces developing countries to search for effective mechanisms

Abstract

The current patentability standards for pharmaceutical inventions, as well as strategic patenting used by pharmaceutical companies, have substantially impacted access to affordable medicines. This has been especially detrimental for developing countries, which are under significant pressure to remain compliant with their international and bilateral obligations, while also providing their people with essential drugs. In order to improve access to medicines, developing countries may choose from a range of various mechanisms that may help to facilitate such access, while also allowing them to remain compliant with their international and bilateral obligations. This policy brief suggests that one of such mechanisms is to strengthen the obviousness requirement by applying the ‘obvious to try with a reasonable expectation of success’ test to pharmaceutical follow-on inventions. It is argued that the application of this test may be an effective tool in addressing the negative effect of strategic patenting. It may help to prevent the extension of patent protection and market exclusivity of existing drugs by pharmaceutical companies and, as a result, may open such medicines up to generic competition.

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that will facilitate access to affordable medicines, while at the same time allowing them to stay compliant with their obligations. To achieve this, some developing countries have implemented certain measures that are aimed at reducing the negative effect of strategic patenting.¹² While some of these mechanisms may be considered as the effective utilisation of the TRIPS Agreement's flexibilities,¹³ some studies suggest that, in reality, these measures may have limited impact.¹⁴ In addition, various suggestions on how to facilitate access to medicines have been put forward. These include, *inter alia*, such measures as excluding some pharmaceutical follow-on inventions from patent protection,¹⁵ utilising competition law against the strategic use of the patent system,¹⁶ and price regulation.¹⁷

This policy brief offers an additional tool for dealing with strategic patenting that has the potential of reducing its negative effect. It suggests strengthening the inventive step requirement for pharmaceutical follow-on inventions by applying the 'obvious to try with a reasonable expectation of success' test. It is believed that a rigorous application of this test could provide an effective mechanism of opposing strategic patenting, which, in turn, would facilitate access to medicines. The brief will be structured in the following manner. It will first discuss various types of pharmaceutical patents and follow-on inventions, as well as explaining the current approach to the patentability of this type of invention. It will further discuss the 'obvious to try with a reasonable expectation of success' test and will provide examples of how it is applied to pharmaceutical follow-on inventions by the courts in the UK and US. The brief will conclude with some suggestions.

1. Types of pharmaceutical patents and follow-on inventions

Before discussing the inventive step test, it is first important to understand how strategic patenting operates and what effect it may have on access to medicines. New active substances are often patented at an early stage of research and development. Such substance patents are typically called 'basic' or 'primary' patents and provide the strongest protection for pharmaceutical products.¹⁸ After discovering an active compound, the research into this compound often continues as companies search for improvements, new uses, new forms and combinations of already existing drugs. This is due to a unique feature of pharmaceuticals, as an active ingredient may exist in different physical forms and formulations, may have different uses and may be manufactured by different processes. For example, some compounds may exist in different polymorphic forms, such as crystalline and amorphous forms as well as solvate and hydrate forms,¹⁹ which is an inherent property of these compounds.²⁰ An active ingredient of a drug may also exist in a neutral form (free base), or its derivative in the form of a specific salt.²¹ In addition, many pharmaceutical active compounds exist as a racemate, and can be separated into two enantiomers that

may have different therapeutic effects.²² Also, an active ingredient may be produced in various formulations and administered, for example, as tablets or capsules; it may also have different release methods such as, for example, immediate or extended, etc.²³ Moreover, some drugs may exist in an inactive form, so-called prodrugs, and, when taken by the patient, they break down in the body forming metabolites, one of which transforms into an active ingredient with therapeutic effect.²⁴ Finally, pharmaceutical companies typically continue to research existing drugs for potential new medical uses for the treatment of a different disease or condition.²⁵

Once these new forms, formulations, uses and processes of a known active ingredient are discovered, a pharmaceutical company would usually seek patent protection on these modifications.²⁶ As such modifications would typically be discovered at a later stage of research into active compounds, patents that protect them are often called 'follow-on' or 'secondary' patents.²⁷ The typical lifecycle strategy is to file for patents on these follow-on inventions several years after the basic product patent was obtained.²⁸ Such a strategy has the capacity to significantly extend the market exclusivity of a pharmaceutical product beyond the term of protection provided by the basic patent.²⁹

2. Patentability of pharmaceutical inventions: inventive step analysis

Most international instruments, including the TRIPS Agreement³⁰ and national laws,³¹ require that, for an invention to be patented, it must meet specific patentability requirements. This typically means that the invention must be new, non-obvious and industrially applicable, and that it must not fall within the list of excluded subject matter. One of the most important patentability requirements is 'inventive step', also called 'obviousness', as its fundamental function is to ensure that patents are granted to only genuine inventions.³² The main question at this stage is whether the invention would have been obvious to the person skilled in the art at the time of the invention.³³ While being one of the most important stages of the patentability analysis, the assessment of the inventive step is also one of the most difficult and problematic exercises, because it is typically based on the specific facts of each case and involves, to some extent, a subjective judgement of what is or is not obvious.³⁴ The application of the obviousness requirement may result in either granting a secondary patent on, for example, a new salt of a known active compound, or finding that this follow-on invention is obvious, and thus rejecting patent protection. Therefore, rigorous application of the obviousness requirement may help to avoid granting protection to insignificant and trivial modifications, which, while providing no benefit to society, may stifle generic competition and block further innovation.³⁵

2.1. Current approach to the 'inventive step' analysis of pharmaceutical follow-on inventions

The pharmaceutical industry is generally perceived as

unpredictable.³⁶ Thus, when searching, for example, for a polymorphic form or a salt of a drug, it is difficult to predict in advance which form or salt will be the most pharmaceutically suitable.³⁷ These considerations often underpin the obviousness analysis of follow-on pharmaceutical inventions. The patent offices and the courts, including in the UK and US, allow patents on follow-on inventions, emphasising the importance of unpredictability.³⁸ The prevailing view is that, as it is impossible to foresee whether a specific solid form, salt, enantiomer, etc. will possess a desired quality, such follow-on inventions are the result of trial and error or serendipity and are therefore inventive.³⁹ For example, in *Eli Lilly v Generix Drug Sales*, the court noted that, until science has advanced to a level where it is possible to predict 'with some minimal reliability' the property and therapeutic value of an enantiomer, it will be considered inventive.⁴⁰ Such an approach seems to imply an almost automatic conclusion of non-obviousness. This sets the obviousness requirement extremely low, potentially rendering the majority of follow-on pharmaceutical inventions patentable, because, in most cases, it would be impossible to predict in advance what qualities a researched compound will have. Therefore, on the basis of the above arguments, patents on incremental changes – such as, for example, new salts, polymorphs and enantiomers – are regularly granted by the patent offices, as it is difficult to predict the characteristics of the invention in advance.⁴¹

Nevertheless, some courts have developed a more rigorous obviousness test that raises the patentability standards for pharmaceutical follow-on inventions by applying the 'obvious to try with a reasonable expectation of success' test. The following sections will explain the essence of this test and will provide some examples from case law on how the courts in the UK and US apply this test to follow-ons.

2.2. Defining the 'obvious to try with a reasonable expectation' test

One of the main stages of pharmaceutical research includes experimenting in order to determine whether a selected compound has desired therapeutic properties. Some compounds may have such properties, which may subsequently be useful in treating certain diseases. However, it is only through experiments and testing that one can establish whether they are effective and safe, or whether they turn out to have major side effects. It may sometimes be difficult, or even impossible, to predict with precision which of the selected compounds would have such desired effects. In such cases, some courts apply a two-prong analysis: (a) was it 'obvious to try' for the person skilled in the art, and (b) was there a reasonable expectation of success?

Thus, the first prong of the test, the 'obvious to try' element, deals with situations where it is obvious to try a particular route or method. As the Federal Circuit noted, '[a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity,

such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.'⁴² The following example given by the court in *In re Merck* may be useful to understanding this argument:⁴³

Consider, for example, the Petersen reference which ... demonstrate[s] the possibility that a nitrogen atom may be replaced by a double-bonded carbon atom. This journal article records an attempt to find drugs useful for the treatment of endogenous psychoses, i.e., tranquilizers. The researchers tested eighteen chemicals with closely related structures. These materials were injected into mice, and compared for their ability to make the mice fall asleep. The results of these tests may be tantalizing and useful, but only as a guide for further research. I agree that, based on this information and the other references cited by the board, the researcher with ordinary skill in the art would be motivated to investigate the possibility of substituting a double-bonded carbon atom for nitrogen. The researcher would also be motivated to test every other structural variation in Petersen, as well as a host of others.

This part of the test, therefore, means that, if a route or method was obvious to try, the skilled person will be motivated to try it. However, that does not mean that he will succeed.⁴⁴ Therefore, the 'obvious to try' part is frequently applied in combination with 'a reasonable expectation of success' analysis. This means that, if the person skilled in the art, while taking an 'obvious to try' route or method, also expects that it will work, then the outcome will be obvious.⁴⁵ This, however, does not equate to a certainty and means that the person skilled in the art before commencing a piece of research will be able to predict the likelihood of a successful outcome on the basis of existing knowledge at that time.⁴⁶ For example, when revoking a patent for lack of inventive step, the Hague Regional Court of Appeal explained in *Accord v AstraZeneca* that 'an invention was obvious ... if there was a reasonable expectation of success, i.e. the skilled person could reasonably predict that a research project would be successfully completed within an acceptable timeframe. A mere 'hope to succeed' was insufficient.'⁴⁷ On the other hand, as LJ Floyd held in *Gedeon Richter v Bayer Schering*, if in order 'to arrive at the invention, the skilled person has to embark on an experiment or series of experiments where there was no fair expectation of success, the conclusion will generally be that the invention was not obvious.'⁴⁸ Therefore, the obviousness may be found when it can be shown that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success.⁴⁹

2.3. Applying the 'obvious to try with a reasonable expectation of success' test: the UK and the US experience

While, in general, the 'unpredictability' feature of phar-

maceuticals prevails in the obviousness analysis, some courts in the UK and US have assessed pharmaceutical follow-on inventions using a more rigorous obviousness approach by applying the 'obvious to try with a reasonable expectation of success' test to this type of invention. The application of this test has led to findings of obviousness of follow-ons in these cases, because the skilled person was motivated to pursue the chosen route, and hence it was 'obvious to try', and in light of the prior art, it was reasonable to expect that this route would work. This section will discuss some examples from case law of how the UK and US courts applied this test to pharmaceutical follow-on inventions.

2.3.1. US

In the US, the Federal Circuit in *Pfizer v Apotex* considered whether a patent for the besylate salt of amlodipine was inventive.⁵⁰ The district court found the patent to be non-obvious based on the unpredictable nature of salts. It stated that 'there would be no expectation of success in making a besylate salt of amlodipine because, as [the prior art] teaches and expert testimony on both sides accepted "there is no reliable way of predicting the influence of a particular salt species on the behaviour of a parent compound".⁵¹ However, the Federal Circuit rejected this approach and reversed the decision, finding the patent obvious. While the court acknowledged that, 'in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be',⁵² it stated, however, that 'obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'⁵³ The court further noted that 'this is not the case where there are "numerous parameters" to try', but '[r]ather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt.'⁵⁴ Thus, the Federal Circuit, in this case, found the salt patent invalid because while it was impossible to predict with precision whether a particular salt would have a desired pharmaceutical effect, when searching for such a salt there was a reasonable expectation of success.

This line of argument was followed in a number of subsequent decisions.⁵⁵ For example, in *Allergan, Inc. v Sandoz, Inc.*, the Federal Circuit found the drug Combigan for the treatment of glaucoma obvious and rejected a district court's non-obviousness conclusions on the basis of unpredictability.⁵⁶ The patent in suit protected a combination of the well-known alpha2-agonist brimonidine and the well-known beta-blocker timolol, both of which are also used to treat glaucoma.⁵⁷ The combination also contained the preservative benzalkonium chloride (BAK), which is also widely used in ophthalmic formulations.⁵⁸ While the Federal Circuit acknowledged that 'formulation science carries with it a degree of unpredictability, nevertheless "obviousness cannot be avoided simply by a showing of some degree

of unpredictability in the art so long as there was a reasonable probability of success".⁵⁹ Therefore, the court found that, in light of the prior art, 'one of ordinary skill would have a reasonable expectation of success in formulating a fixed combination product containing brimonidine, timolol, and BAK.'⁶⁰ As in *Pfizer v Apotex*, discussed earlier, the court disregarded the 'unpredictability' argument and considered that the patent was obvious, because it was obvious to try and it was reasonable to expect that the combination of known compounds would work.

2.3.2. UK

A similar logic was relied upon by the UK courts in several recent cases related to follow-on inventions. For example, in *Hospira v Genentech*,⁶¹ the dispute related to formulation patents on the breast cancer drug trastuzumab (Herceptin). In this case, the patentee argued that '[t]he task of formulating proteins was a difficult and unpredictable one and often encountered dead ends' and that '[i]n the absence of anything in the prior art or the common general knowledge to lead the skilled person to expect that the claimed combination would have a beneficial property, the necessary fair expectation of success was not present.'⁶² However, the Court of Appeal disagreed and confirmed the findings of the first instance court, which was that the patents were obvious. The court stated that the claimed formulations would be 'obvious to try' to any skilled person who is motivated to produce a stable dry formulation, and therefore 'there was no invention in embarking on a screening process' to select the most suitable one.⁶³ Moreover, the court stated that 'in an empirical field it will be seldom possible to predict in advance that any individual experiment will work.'⁶⁴ Therefore, the court stated that it would be 'wholly unrealistic' to require that the skilled team must be able to predict in advance the successful combinations.⁶⁵ This 'would lead to the grant of patents for a whole variety of combinations which in fact involved no inventive effort.'⁶⁶ Thus, in this case, the court considered that the skilled person would be motivated to search for an improved formulation, which was indication that these formulations were 'obvious to try' and there was a reasonable expectation of success.

A similar line of argument was followed in the recent *Actavis v ICOS* case, which concerned a dosage patent. The patent claimed a product which comprises 1 to 5 mg of tadalafil and which is suitable for oral administration up to a maximum total dose of 5mg per day.⁶⁷ The prior art did not specifically disclose a 5mg daily dose of tadalafil or that such a dose is an effective treatment for sexual dysfunction.⁶⁸ The court of first instance held that the invention was non-obvious because, inter alia, it was impossible to predict whether the specific dose would work.⁶⁹ However, the Court of Appeal disagreed. It stated that '[t]he fact that the skilled team could not make any prediction at the outset that a dose of 5mg of tadalafil per day would be safe and efficacious is of little weight', because the purpose of the routine clinical trials is to 'understand the dose response relationship of the drug and so identify the appropriate dose range...'.⁷⁰ The court found that 'the

claimed invention lies at the end of the familiar path through the routine pre-clinical and clinical trials' process. The skilled but non-inventive team would embark on that process with a reasonable expectation of success and in the course of it they ... would have arrived at the claimed invention.⁷¹ Thus, the court considered that searching for a suitable dose of a known compound is a routine procedure and that, when embarking on such a procedure, there is a reasonable expectation of success.

It is also interesting to mention some observations made by the UK Supreme Court in the recent *Actavis v Eli Lilly* case, which also seems to support this approach.⁷² While the dispute was focused on whether the competing product that uses different salts than the patented product falls within the patent claims,⁷³ the court also made several important observations in relation to the 'unpredictability' of salts. When discussing the common general knowledge, the court noted that, 'a chemist "would not be able to predict the effect of [a] substitution [for the sodium counter-ion] without testing at least the solubility of the [active ingredient in the Actavis products]"', it followed that "predicting in advance whether any particular counter-ion would work was not possible".⁷⁴ Nevertheless, the court stated that 'salt screening is a routine exercise in determining suitability ... "the chemist would be reasonably confident that he would come up with a substitute for the sodium counter-ion".'⁷⁵ This statement supports the view that, in the area of pharmaceutical follow-on inventions, a successful outcome in finding of a suitable salt can be reasonably expected.

2.4. Take-aways of the discussed case law

The above case law demonstrates that, when assessing pharmaceutical follow-on inventions, the patent can be found obvious if it can be shown that it was 'obvious to try' a specific route and there was a reasonable expectation of success that this would lead to a positive result. Moreover, as can be seen from the discussion of the case law, the requirements for both parts of the test have been set at a low level. Thus, the general motivation of a skilled person to pursue a certain route or method based on prior art – which may be prompted by, for example, a general desire to improve the drug – was considered sufficient to find 'obvious to try'.⁷⁶ In addition, the absolute and specific prediction of success was also not required. For example, the court in *In re O'Farrell* stated that '[o]bviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice.'⁷⁷

While this approach provides a strict patentability standard for pharmaceutical follow-on inventions, the support for utilising such an approach can be drawn from the notion that, in the mature field of pharmaceuticals, follow-on inventions typically build upon and modify an existing successful drug, applying tech-

niques well-known to the person skilled in the art.⁷⁸ Thus, research into incremental improvements, such as finding a suitable salt, dosage, enantiomer, etc., is, in general, a routine procedure in the pharmaceutical field, typically initiated because it is 'obvious to try' and pursued with 'a reasonable expectation of success'. Therefore, a rigorous application of the 'obvious to try with a reasonable expectation of success' test by the patent offices and the courts in many cases may lead to finding such follow-on inventions obvious.

3. The 'obvious to try with a reasonable expectation of success' test may assist developing countries in facilitating access to medicines

As was discussed at the beginning of this policy brief, the current patentability standards for pharmaceutical inventions, as well as strategic patenting used by pharmaceutical companies, have substantially impacted access to affordable medicines. This has been especially detrimental for developing countries, which are under significant pressure to remain compliant with their international and bilateral obligations, while at the same time have been struggling to provide their people with essential drugs. In order to improve access to medicines developing countries may choose from a range of various mechanisms that may help to facilitate such access, while also allowing them to remain compliant with their international and bilateral obligations. One of such mechanisms is to apply a strict patentability standard for pharmaceutical follow-on inventions. This can be done by relying on the 'obvious to try with a reasonable expectation of success' test to this type of invention. On the basis of the above discussion, this brief suggests that the application of this test may be an effective tool in addressing the negative effect of strategic patenting. In particular, it may help to reduce the number of secondary patents related to minor modifications of existing drugs, such as, for example, salts, polymorphs, enantiomers and various formulations.⁷⁹ This, in turn, may help to prevent the extension of patent protection and market exclusivity of existing drugs by pharmaceutical companies, and thus may open such medicines up to generic competition.

Importantly, such an approach will be in line with the TRIPS Agreement. While the TRIPS Agreement made the provision of patent protection for drugs mandatory, it did, nevertheless, allow its Member States to define the degree of such protection by setting the level of the patentability standards for this type of invention in their national patent laws.⁸⁰ In addition, when setting such patentability requirements, the TRIPS Agreement specifically allows the Member States to take into account not only the interests of patent holders, but also other various public interests and objectives.⁸¹ In particular, Article 8 states that '[m]embers may, in formulating or amending their laws ..., adopt measures necessary to protect public health...'. Utilising the 'obvious to try with a reasonable expectation of success' test will be in line with the cited provisions. Specifically, providing patent protection for

drugs is in accordance with Article 27 of TRIPS, while adopting a higher patentability standard for pharmaceutical follow-on inventions is compliant with the provisions of Article 8. Therefore, such an approach to pharmaceutical follow-on inventions may help developing countries to facilitate access to medicine, while also allowing them to remain compliant with their obligations under the TRIPS Agreement and other bilateral obligations that require providing patent protection for pharmaceutical inventions.

Conclusion

The obligation to introduce patent protection on medicines as mandated by the TRIPS Agreement, its further strengthening by bilateral trade agreements, and the strategic use of the patent system by pharmaceutical companies have, together, significantly impaired the ability of developing countries to provide their citizens with affordable life-saving medicines. While they are bound by their obligations to operate within these strict limitations, some mechanisms may help developing countries to improve access to affordable medicines. In particular, this brief suggests that a strict patentability requirement may become a useful tool in addressing strategic patenting that is aimed at extending market exclusivity of an existing drug beyond its basic patent. As was explained, secondary patents protect minor and insignificant modifications and have the capacity to extend the life of a product considerably. It is, therefore, suggested that the application of the 'obvious to try with a reasonable expectation of success' test to this type of pharmaceutical follow-on invention may reduce the number of secondary patents and provide access to affordable medicines by facilitating generic competition.

Endnotes:

¹ Cynthia M. Ho, "Should All Drugs Be Patentable?: A Comparative Perspective", *Vanderbilt Journal of Entertainment & Technology Law*, vol. 17, No 2 (2015) 306 ('One traditional exclusion from patentable subject matter for many countries was an exclusion of drug and drug components because the higher cost of patented drugs would limit access to affordable medicine').

² Ho (n 1) 306; Olga Gurgula, "Monopoly v. Openness: Two sides of IP coin in the pharmaceutical industry", *JWIP*, vol. 20, No 5-6, 207.

³ Article 27(1) of the Treaty on Trade Related Aspects of Intellectual Property Rights, an annex to the World Trade Organisation Agreement (1994) (TRIPS) (emphasis added).

⁴ María José Abud Sittler, Christian Helmers and Bronwyn Hall, 'Study On Pharmaceutical Patents In Chile' *Committee on Development and Intellectual Property (CDIP)* (Fifteenth Session, Geneva, April 20 to 24, 2015) (discussing that 'during the negotiations of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, pharmaceutical product patents represented one of the most divisive issues, being opposed by developing countries because of concerns that stronger patent protection would hinder access to drugs and prevent the de-

velopment of a domestic pharmaceutical industry').

⁵ Sisule F. Musungu, Susan Villanueva and Roxana Blasetti "Utilizing TRIPS Flexibilities for Public Health Protection through South-South Regional Frameworks" *South Centre* (April 2004) 30.

⁶ *ibid.*

⁷ Inderjit Singh Bansal and others, "Evergreening - A Controversial Issue in Pharma Milieu", *Journal of Intellectual Property Rights*, vol. 14, 299.

⁸ UNCTAD, 'The role of competition in the pharmaceutical sector and its benefits for consumers' (2015) TD/RBP/CONF.8/3, 6.

⁹ European Commission, 'Pharmaceutical Sector Inquiry Final Report' (8 July 2009)
<http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf> (accessed 15 March 2019) ('Pharma Report').

¹⁰ European Commission, 'Executive Summary of the Pharmaceutical Sector Inquiry Report' (8 July 2009) 10
<http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf> (accessed 15 March 2019).

¹¹ *ibid.*

¹² Carlos M Correa, *Pharmaceutical innovation, incremental patenting and compulsory licensing* (South Centre, 2013); D.B Barbosa, "Patents and the Emerging Markets of Latin America: Brazil" in *Emerging Markets and the World Patent Order*, Frederick M. Abbott, Carlos M. Correa and Peter Drahos, eds. (Edward Elgar Publishing, 2015) 135-151; Shamnad Basheer and Prashant Reddy, "The 'Efficacy' of Indian Patent Law: Ironing out the Creases in Section 3(d)", *Scripted*, vol. 5, No 2 (2008)
<<https://ssrn.com/abstract=1086254>> (accessed 15 March 2019).

¹³ Patents Act, 1970, § 3(d), amended by Patents (Amendment) Act, 2005.

¹⁴ Bhaven N Sampat and Kenneth C Shadlen, "Secondary pharmaceutical patenting: A global perspective", *Research Policy*, vol. 47, No 3 (2017), 693.

¹⁵ Carlos M. Correa, 'Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective' UNDP (2015)
<http://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP_patents_final_web_2.pdf> (accessed 15 March 2019) 18 (*Guidelines for Pharmaceutical Patent Examination*).

¹⁶ Duncan Matthews and Olga Gurgula, "Patent Strategies and Competition Law in the Pharmaceutical Sector: Implications for Access to Medicines" *European Intellectual Property Review*, vol. 38, No 11 (2016); Pharma Report (n 9); Frederick M. Abbott and others "Using Competition Law to Promote Access to Health Technologies: A Guidebook for Low- and Middle-Income Countries" United Nations Development Program (May 19, 2014)
<<https://ssrn.com/abstract=2439416>> (accessed 15 March 2019).

¹⁷ Aaron S Kesselheim and others, "The High Cost of Prescription Drugs in the United States Origins and Prospects for Reform", *JAMA*, vol. 316, No 8 (2016), 858.

¹⁸ COMP/A. 37.507/F3 - AstraZeneca [2005], para 14.

¹⁹ FDA, "Guidance for Industry. ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information" (2007) 1
<<https://www.fda.gov/downloads/drugs/guidances/ucm072866.pdf>> (accessed 15 March 2019) ('A drug substance may exist in many polymorphic forms') 2.

²⁰ Dennis Douroumis and Ali Nokhodchi, "Preface: Engineering of pharmaceutical cocrystals, salts and polymorphs: Advances and Challenges", *Advanced Drug Delivery Reviews*, vol. 117, (2017) 1; *Guidelines for Pharmaceutical Patent Examination* (n 15) 25; Roberta Censi and Piera Di Martino, "Polymorph Impact on the Bioavailability and Stability of Poorly Soluble Drugs", *Molecules*, vol. 20, No 10 (2015) 18765 (more than 60 polymorphic forms have been patented in relation to atorvastatin calcium, a blockbuster drug sold under the brand name Lipitor used in the treatment of cardiovascular diseases).

²¹ David P. Elder and others, "Use of pharmaceutical salts and cocrystals to address the issue of poor solubility", *Int. J. Pharm.*, vol. 453, No 1 (2013) 88 ('Salt and cocrystal formation are the most commonly used method of increasing solubility and dissolution rate of pharmaceutical compounds').

²² *Lundbeck A/S v. Neolab Ltd. et al.* (Escitalopram), invalidity proceedings, Federal Supreme Court, Germany, 10 September 2009, Docket number Xa ZR 130/07, para 10 ('Enantiomers ... are molecules that have the same structure and differ from one another solely in the spatial arrangement (configuration) of the individual atoms. Enantiomers differ from one another like mirror images').

²³ Hao Yin, "A new formula for analyzing formulation-patent obviousness", *Temple Law Review*, vol. 83 (2011) 831.

²⁴ Rebecca S. Yoshitani and Ellen S. Cooper, "Pharmaceutical Reformulation: The Growth of Life Cycle Management", *HOUS. J. HEALTH L. & POL'Y*, vol. 7, (2007) 389. For example, descarboethoxyloratadine is an active metabolite of an antihistamine drug loratadine.

²⁵ One of the famous examples of such a new use is a drug Viagra that was originally developed to treat heart disease.

²⁶ Trevor Cook, *A User's Guide to Patents* (4th Edn, Bloomsbury, 2015) 373.

²⁷ As the EU Commission explained in its Pharma Report (n 9): 'At some point during the lead identification/optimisation process, a company will begin to consider filing a patent application. Initially, these applications will be concerned with the active molecules themselves. The applications, and the resulting patents, are often referred to as "primary patents" because they relate to the first patents for the active molecules. Later during the development phase and, ... not uncommonly after the product launch, further patent applications will be made for other aspects of these active molecules, such as different dosage forms (e.g. tablets, capsules or solutions for injection) or for particular pharmaceutical formulations (mixtures of active agents and other substances which promote the activity of the medicine by, for example, enhancing absorption in the body).

²⁸ Walter Cabri and others, "Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study", *Organic Process Research & Development*, vol. 11, No 1 (2007) 64.

²⁹ *ibid.*

³⁰ Article 27 TRIPS.

³¹ See e.g. Article 1(1) of the Patent Act 1977 (as amended).

³² *ibid.*

³³ EPO, 'Guidelines for Examination in the European Patent Office' (November 2017 edn.) Part G – Chapter VII-3 Section 4 ('... whether before the filing or priority date valid for that claim, having regard to the art known at the time, it would have been obvious to the person skilled in the art to arrive at

something falling within the terms of the claim. If so, the claim is not allowable for lack of inventive step').

³⁴ Philip W. Grubb and others, *Patents for Chemicals, Pharmaceuticals, and Biotechnology. Fundamentals of Global Law, Practice and Strategy* (6th edn, OUP, 2016) 71-72.

³⁵ *Guidelines for Pharmaceutical Patent Examination* (n 15) 14.

³⁶ Clark Sullivan and Michael Kline, "Introduction to Patentability in Drug Development" (Future Science Ltd, 2016) 90 ('it is not possible to predict pharmaceutical activity *ab initio*').

³⁷ Edyta Pindelska and others, "Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques", *Advanced Drug Delivery Reviews*, vol 117 (2017) 112 ('It is a challenge for pharmaceutical research and industry to find appropriate drug cocrystal combinations, salts or polymorphic forms for the therapeutic and pharmaceutical market').

³⁸ Frederick G. Vogt, "Unexpected Results: The Current Status of Obviousness Determinations for Pharmaceutical and Biotechnology Patents", *Temp. J. Sci. Tech. Envtl. L.*, vol. 29 (2010) 330.

³⁹ Michael Enzo Furrow, "Pharmaceutical Patent Life-Cycle Management after KSR v. Teleflex", *Food & Drug L.J.*, vol. 63, No 1 (2008) 294; Christopher Holman and others, "Patentability Standards for Follow-On Pharmaceutical Innovation", *Biotechnology Law Report*, vol.37, No 3 (2018) 152.

⁴⁰ *Eli Lilly & Co., Inc. v. Generix Drug Sales, Inc.*, 460 F.2d 1096, 1103 (5th Cir. 1972).

⁴¹ Vogt (n 38) 326

⁴² *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed.Cir. 1990).

⁴³ *In re Merck & Co.*, 800 F.2d 1091, 1100 (Fed. Cir. 1986)

⁴⁴ Mark A. Lemley, "Expecting the Unexpected", *Notre Dame L. Rev.*, vol. 92 (2017) 1374.

⁴⁵ *ibid* 1370.

⁴⁶ Manfred E. Wolff, "Drug discovery market exclusivity after KSR: The challenge to pharmaceutical scientists and the US congress", *Wiley Online Library* (2011) 3046-3047 (wileyonlinelibrary.com). DOI 10.1002/jps.22564

⁴⁷ The Hague Regional Court of Appeal of 10 June 2014 – *Accord v AstraZeneca*. See also "Case Law of the Boards of Appeal", 7th ed. 2013, chapter I.D.7; Supplementary publication 2/2015 – Official Journal EPO, V. EUROPEAN PATENTS SUBJECT TO LITIGATION IN MULTIPLE JURISDICTIONS, available <<http://www.epo.org/law-practice/legal-texts/official-journal/2015/etc/se2/p132.html#qsalt>> citing Federal Court of Justice of 15 May 2012 (X ZR 98/09) – *Calcipotriol monohydrate* 'it might be relevant to consider whether the skilled person could reasonably have expected that such action would successfully solve the technical problem') (accessed 15 March 2019).

⁴⁸ [2011] EWHC 583 (Pat) para 113.

⁴⁹ EPO Case Law of the Boards of Appeal (8th edn, 2016) Chapter I D, para 7.1.

⁵⁰ *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 1370 (Fed.Cir. 2007) (*Pfizer v Apotex*).

⁵¹ *ibid*, at 1357.

⁵² *ibid*, at 1364.

⁵³ *ibid* (internal citation omitted).

⁵⁴ *ibid*, at 1366.

⁵⁵ See e.g. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326 (2014).

⁵⁶ 726 F.3d 1286 (Fed. Cir. 2013).

⁵⁷ *ibid.*, at 1289.

⁵⁸ *ibid.*

⁵⁹ *ibid.*, 1292 citing *Pfizer v Apotex* (n 50).

⁶⁰ *ibid.*

⁶¹ *Hospira UK Ltd v Genentech Inc* [2017] R.P.C. 13.

⁶² *ibid.*, [30].

⁶³ *ibid.*, [52].

⁶⁴ *ibid.*, [51].

⁶⁵ *ibid.*

⁶⁶ *ibid.*

⁶⁷ *Actavis Group PTC EHF v ICOS Corp* [2017] EWCA Civ 1671; (2018) 159 B.M.L.R. 108 (*Actavis v ICOS*) [38].

⁶⁸ *ibid.*, [105].

⁶⁹ [2016] EWHC 1955 (Pat); [2016] 8 WLUK 146.

⁷⁰ *Actavis v ICOS* (n 67), [147].

⁷¹ *ibid.*, [152].

⁷² *Actavis UK Ltd v Eli Lilly & Co* [2017] Bus. L.R. 1731.

⁷³ *ibid.*, [1740].

⁷⁴ *ibid.*, [1751] citing Floyd LJ [2015] Bus LR 1068, para 65.

⁷⁵ *ibid.*

⁷⁶ *Teva UK Ltd v Leo Pharma A/S* [2014] EWHC 3096 (Pat) [69]

⁷⁷ *In re O'Farrell*, 853 F.2d 894 (Fed.Cir. 1988), at 903.

⁷⁸ *Guidelines for Pharmaceutical Patent Examination* (n 15).

⁷⁹ Lemley (n 44) 1370; see also Pharma Report (n 9), para 1324 ('in those cases where such patent applications, if granted, could serve to prolong the income stream from a medicine well beyond the expiry of the original patent protection, it is crucial that such an application be scrutinised very carefully and that a patent be awarded only where a true inventive contribution is made').

⁸⁰ UNCTAD-ICTSD, *Resource Book on TRIPS and Development* (Cambridge University Press, 2005) 358 ('This provision sets up the criteria of patentability, without however harmonizing the way in which they have to be implemented. Thus, Members have considerable leeway in applying those three criteria (novelty, inventive step and industrial applicability.'): Hiroko Yamane, *Interpreting TRIPS: globalisation of intellectual property rights and access to medicines* (Hart, 2011) 420.

⁸¹ Ho (n 1) 334.

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