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Sacrificing the Patentability Standard of Novelty and Industrial Application on the Altar of Incremental Biotech Innovation in Hong Kong

ABSTRACT

Dr. Danny Friedmann

Despite non-novelty and the non-susceptibility of industrial application for a diagnostic, therapeutic or surgical treatment, most jurisdictions, including Hong Kong, have chosen to allow first and further medical use claims. Hong Kong's new patent system includes for the first time in its history the possibility of applying for an Original Grant Patent. It is expected that the Patent (Amendment) Bill 2015 will come into effect in 2018. This article first focuses on the patentability requirements for medical use claims, their failure and solution. Like an alchemist who is forging gold out of lead, the new Hong Kong patent ordinance purifies the failures of these patentability requirements by using two fictions (Sections 9(B)(5) and 93(4) Patents Ordinance). After this doctrinal hurdle is overcome, the Hong Kong patent system pragmatically allows for straightforward purpose-limited claims, but also for Swiss-type claims. Even though Hong Kong followed the UK and EPO in accepting the Swiss-type claim, it does not follow them in their rejection of this convoluted claim, because Hong Kong's patent system wants to continue to be able to re-register Chinese innovation patents that are phrased as Swiss-type claims.

The advantages and disadvantages of first and further medical use, methods of delivery and patient groups are explored. In case of a slew of ever more obscure uses, it seems, at least *prima facie*, the scales are tipped towards protection of extending originators' patent rights which is not conducive for generics and the access to reasonably priced medicines, but might be positive for efficacy studies.

The article will pose the age old question as well: will a patent-friendly but potentially access-unfriendly approach harness or harm innovation in biotech? Here a distinction will be made between the different kinds of innovation, such as claims for polymorphs, enantiomers (optical isomers), salts, ethers, esters, compositions, doses, prodrugs, metabolites, analogy processes, and Markush and selection claims. The article will explore the possibility of reconciling the granting of patents for second and further medical use claims with an enhanced efficacy and utility regime conform the respective Canadian and Indian legal innovations, so that at least these medical uses will demonstrate incremental but observable improvements for patients.

Sacrificing the Patentability Standard of Novelty and Industrial Application on the Altar of Incremental Biotech Innovation in Hong Kong

Dr. Danny Friedmann*

Section 1. Introduction

“And while he dreams of finding in the fire
that true gold that will put an end to dying,
God, who knows His alchemy, transforms him
to no one, dust, oblivion.”¹

The rationale behind the grant of an invention patent, an exclusionary right limited in scope, duration and effect,² provides on the one hand an incentive to innovate for individuals, and on the other hand procures information for the rest of the industry, which must help elevate the level of innovation in society.³ Or to put it eloquently as Peter Rosenberg: “the inventor makes a truly Faustian bargain”,⁴ by removing the necessity of obfuscating the invention,⁵ disclosing the invention⁶ in a formalised way so that a person skilled in the art will know how to practise it,⁷ in return for a patent. Does society make an even more Faustian pact in the case of biomedical

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¹ Jorge Luis Borges, *SELECTED POEMS, VOLUME 2, The Alchemist* (Penguin Books: London, 2000) 223, last paragraph.

² The question with, for example, genetic diagnostics methods is whether a second opinion, where another laboratory needs to resequence the patient’s genes, exhausts the patent or not. See Kevin Noonan, *The Relevance of Patent Exhaustion in the Myriad Genetics Case*, PatentDocs, 14 December 2010, available at: <http://www.patentdocs.org/2010/12/the-relevance-of-patent-exhaustion-in-the-myriad-genetics-case.html>. Arti K. Rai, *Diagnostic Patents at the Supreme Court*, 2013 Annual Helen Wilson Nies Lecture, 18 MARQ. INTEL. PROP. L. REV. 1, available at: <https://pdfs.semanticscholar.org/1108/2cf9f6786457e5e1b068ced18499ba613f0e.pdf>. Paul Veravanich and John Kappos, *Is The Supreme Court Exhausted With Patents?* Orange County Business Journal, 2 September 2008, available at: <https://www.omm.com/files/upload/IsTheSupremeCourtExhaustedWithPatents.pdf>.

³ William Cornish, David Llewelyn and Tanya Aplin, *INTELLECTUAL PROPERTY: PATENTS, COPYRIGHT, TRADE MARKS AND ALLIED RIGHTS* (8th edition, Sweet & Maxwell: London, 2013) 143.

⁴ “The purpose of disclosure to the public is to catalyze other inventors into activity. ... The inventor makes a truly Faustian bargain with the sovereign, exchanging secrecy of indefinite and of possibly perpetual duration, for ephemeral patent rights.” Peter Rosenberg, *PATENT LAW FUNDAMENTALS*, Clark Boardman Co. 1975, 7.

⁵ One could also consider alternative ways to incentivize inventors to invent; including direct grants, patent pools and public databases.

⁶ Devlin argues that in case of conflicts between the incentivize-to-invent doctrine and the disclosure doctrine, the first should prevail, since the latter is merely ancillary to the first. Alan Devlin, *The Misunderstood Function of Disclosure in Patent Law* (2010) 23(2) *HARVARD JOURNAL OF LAW AND TECHNOLOGY* 401.

⁷ Sven Bostyn, *Enabling Biotechnological Inventions in Europe and the United States. A study of the patentability of proteins and DNA sequences with special emphasis on the disclosure requirement*, Eposcript Series, no. 4, EPO, München, 2001, *passim*.

pharmaceuticals? In its quest for knowledge to raise the state of the art, does it sell its soul by granting patents to exclude others from accessing, for two decades, the patented medical inventions and protecting a premium price for patented medicines?⁸ However, one can also argue that the patent system helps inventors as a Smithian hand to coordinate their efforts and explore alternative solutions by working around existing patents.⁹ In principle, after the patent has expired, pharmaceutical companies can start manufacturing and selling these generic versions of the medicine. However, this turns out to be often more challenging in practice.¹⁰

Since Hong Kong is a Special Administrative Region of the People's Republic of China, its governance falls under its constitution, which is called the Basic Law. Similar to the Intellectual Property Clause of the U.S. Constitution,¹¹ the Hong Kong government should, on its own, formulate policies on science and technology. Also, it should protect by law the achievements in scientific and technological research, patents, discoveries and inventions.¹² Instead of exclusively re-registering patents from the designated patent offices of China, EPO or the UK, the Patent (Amendment) Bill 2015, which was accepted in 2016 and will go into effect in 2018, will introduce also the possibility of granting an Original Grant Patent. China's State Intellectual Property Office is helping Hong Kong with the acquisition of the knowledge and skills of how to do substantial examinations.¹³ Just as most jurisdictions, Section 93 Patent Ordinance 1997 prescribes the

⁸ In *Myriad Genetics* opponents of patenting isolated natural occurring DNA sequences (such as BRCA1 and BRCA2 that can help detect high risk of breast and ovarian cancer) argued that cancer research would be stifled and limit options for cancer patients in seeking genetic testing. The Supreme Court held that the diagnostic claims were not patent eligible, because they claim genetic information that is produced by nature. In *Association for Molecular Pathology, et al. v Myriad Genetics, Inc., et al.* 133 S.Ct. 2107, 13 June 2013.

⁹ Bostyn and Petit distinguish two forms of 'competition by substitution'; the competition by 'follow on innovators' and that by 'pioneer innovators'. Sven Bostyn and Nicolas Petit, Patent=Monopoly: A Legal Fiction (December 31, 2013), available at: <https://ssrn.com/abstract=2373471>, 7.

¹⁰ Carrier has written about the diverse ways generics are blocked from the market. For example via reverse patent settlements and denying them samples. See the respective articles: Michael Carrier, Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality (2009) 108 MICHIGAN LAW REVIEW 27; Michael Carrier, A Simple Way to Lower Drug Prices, IP Watchdog, 24 June 2016, available at: <http://www.ipwatchdog.com/2016/06/24/simple-way-lower-drug-prices/id=70314/>.

¹¹ Article I, Section 8, Clause 8, of the U.S. Constitution grants Congress the power "[t]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries".

¹² Article 139 Basic Law of Hong Kong S.A.R. of China 1997: "The Government of the Hong Kong Special Administrative Region shall, on its own, formulate policies on science and technology and protect by law achievements in scientific and technological research, patents, discoveries and inventions."

¹³ Danny Friedmann, EDITORIAL: First thoughts on Hong Kong's new patent system; second thoughts on its further medical use claims, 11(12) JOURNAL OF INTELLECTUAL PROPERTY LAW AND PRACTICE (Oxford University Press, 2016) 871-872, <https://academic.oup.com/jiplp/article/11/12/871/2335244/First-thoughts-on-Hong-Kong-s-new-patent-system?keytype=ref&ijkey=hxznYz5HJb8Omj>.

following validity standards for patents; novelty,¹⁴ inventive step,¹⁵ enablement and industrial application. All crucial components in raising the state of the art.

After the introduction (Section 1) above, the article is structured as follows:

Section 2 deals with the methods of medical treatment and diagnostics not susceptible for industrial application;

Section 3 succinctly explores some of the near bioequivalents such as polymorphs, enantiomers and salts, which bring along non-novelty and obviousness challenges;

Section 4 covers claims of the dosage for a known substance and claims for diagnostics for stratified medicine which consist of a known substance;

Section 5. provides the conclusions and suggests the *lex ferenda* for Hong Kong.

Section 2. Methods of medical treatment not susceptible for industrial application

Article 27(3) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allows World Trade Organization members to exclude “diagnostic, therapeutic and surgical methods for the treatment of humans or animals” from patentability. The reason for this possibility is that jurisdictions should be able to immunize their health professionals, such as doctors, hospitals, and indirectly their pharmacists, from the liability of patent infringement.¹⁶ However, many jurisdictions including Hong Kong have decided to tolerate the protection of methods of medical treatment via patents under certain circumstances.

Article 93(4) Patent Ordinance 1997 states that a method for treatment of the human or animal body by surgery or therapy and a diagnostic method practised on the human or animal body shall not be regarded as an invention which is susceptible of industrial application for the purposes of novelty and inventive step.¹⁷ However, the second sentence of Article 93(4) states that deficiencies that would lead to non-susceptibility of industrial application do not apply to a product, and in particular a substance or composition, for use in any such method. Section 9(B)(5) Patents

¹⁴ Although patent rights are territorial, the requirement of novelty of Section 94(2) Patent Ordinance 1997 is tested in relation to the state of the art that comprises everything available to the public in Hong Kong or elsewhere, or anticipated by a person skilled in the art. If an invention has already been claimed in a patent, another patents does not deserve to be registered covering the same claims. In that case, the prior patent holders can make use of the right of priority, according to Article 4(C) Paris Convention for the Protection of Industrial Property and Articles 2 and 29 Agreement on Trade-Related Aspects of Intellectual Property Rights, which can expand their realm of protection within a 12 months after the date of filing the application. Conform Article 153 Basic Law, the Paris Convention also applies to Hong Kong with effect from 1 July 1997 via China’s membership, see Paris Notification No. 178 of 6 June 1997. Conform Article 151 Basic Law, Hong Kong is an independent member of WTO since 1 January 1995, and thus member of the Agreement on Trade-Related Aspects of Intellectual Property Rights, which is an integral part of the Agreement on the World Trade Agreement.

¹⁵ Section 96(1) Patent Ordinance 1997: “An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.”

¹⁶ In the US there is no statutory prohibition against patenting methods of medical treatment. Instead Congress amended the Patent Act in 1996: 35 USC § 287(c), which exempts licensed medical professionals (e.g. doctors) and related health care entities (e.g. hospitals) from liability for infringement of medical method patents.

¹⁷ In *Myriad Genetics* the Supreme Court makes clear that therapeutic method patents are allowed under US patent law. “It is important to note what is not implicated by this decision. First, there are no method claims before this Court. Had Myriad Genetics created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent.” *Supra* note 8. Holbrook concludes that there is differential treatment for method patents. Timothy Holbrook, *Method Patent Exceptionalism* (April 7, 2016). 102 IOWA LAW REVIEW, 2017, forthcoming. Available at: <https://ssrn.com/abstract=2760490>.

(Amendment) Bill 2015 makes clear that first and further medical use of the product/substance or composition will be regarded as new. This legal fiction enables a slew of medical patent claims that, at first sight, seem to protect marginal improvements. Practically, these claims can be drafted via directly phrased purpose-limited product claims¹⁸ or the convoluted Swiss-type claims. Since *Abbott GmbH v Pharmareg Consulting Company Ltd* in 2009,¹⁹ Hong Kong followed the UK and the EPO in allowing Swiss-type claims.²⁰ But when the UK and EPO rejected Swiss-type claims in 2010,²¹ Hong Kong continued to allow these drafts for the re-registration of Chinese patents that were expressed in this sort of claim. Under the amended patent it will allow claims to be drafted in both forms.

To avoid that pharmaceutical companies could register patents for known compounds for new uses to substitute their expired patents (“evergreening”), India amended its law in 2005 by setting an enhanced efficacy standard for these kinds of inventions:

Article 3 Patent (Amendment) Acts 2005: “The following are not inventions within the meaning of this Act, (...)

(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.”²²

It is India’s policy to incentivize the development of medicines that increase efficacy, prevent patent thickets and provide space for generic companies to manufacture inexpensive medicines. Considering the Indian policy, the next section will take the degree of efficacy enhancement into account when analysing new medical uses of known compounds.

Section 3. Bioequivalent or not bioequivalent, that’s the question

Each jurisdiction has to make policy decisions about what kind of patent claims of known compounds used in a new way are acceptable, to what degree and under which conditions? In the case of Hong Kong, this Special Administrative Region wants to be on the one hand a respected member of the international community, and protect the very high investments into research and development by the biotech and pharmaceutical industry, especially since the costs of copying in these industries are particularly low.²³ On the other hand, Hong Kong should also guarantee the

¹⁸ Purpose-limited product claims are drafted in this way: “X for use in the treatment of Y.” See definition and case law at 7.2.3 Purpose-limited product claims and Swiss-type claims – scope of protection, EPO, available at: http://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_i_c_7_2_3.htm.

¹⁹ *Abbott GmbH & Another v Pharmareg Consulting Company Ltd & Another* [2009] 3 HKLRD 524 (HK Court of First Instance).

²⁰ Swiss-type claims are drafted in this way: “Use of X for the manufacture of a medicament for the treatment of Y.” *Supra* note 18.

²¹ *G 0002/08* (Dosage regime/ABBOTT RESPIRATORY) 19 February 2010, ECLI:EP:BA:2010:G000208.20100219.

²² For a comprehensive legal and historical analysis of Section 3(d) Patents (Amendment) Act 2005, see Feroz Ali Khader, *THE ACCESS REGIME: PATENT LAW REFORMS FOR AFFORDABLE MEDICINES* (Oxford University Press, 2016).

²³ This “sweat of the brow” justification - diligence is sufficient, no need for substantial creativity -, originates from Locke. John Locke, *TWO TREATISES OF GOVERNMENT*, Second Treatise of Government, (P. Laslett rev. ed. 1963 3d ed., 1698) 138-140. See Justin Hughes, *The Philosophy of Intellectual Property* (1988) 77 *Geo. L.J.* 287.

access of its population to affordable medicines, which can be expedited by using high patentability standards. To balance these interests, legislators, courts and examiners can mix these interests, using the novelty, inventiveness and industrial application requirements as control sliders.²⁴

As time goes by, most chemical compounds are already part of the prior art. For pharmaceutical companies it becomes ever harder to come up with new compounds. Therefore, pharmaceutical companies who stand on the edge of the patent cliff,²⁵ when their products are about to go off-patent, are looking for ways to patent near bioequivalents.²⁶ Patenting these new uses and forms of known compounds can help them to get a follow-on patent, which can function as a parachute, helping them to delay and soften the landing from the patent cliff.

The challenge for pharmaceutical companies is to convince the patent office of the difference and surprising enhanced efficacy of the new form in comparison to the old form of the known substance. The challenge for patent offices, which are representing the public interest, is to guarantee that pharmaceutical companies are incentivized to invent new medicines, but also to make sure that the public has access to affordable medicines.

An explanation of Section 3(d) Patents Act of India enumerates a list of substances that have similar properties with regard to efficacy:

“salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

Two guidelines for pharmaceutical patent examination, both authored by Carlos Correa in 2015²⁷ and 2006,²⁸ discuss the absence of the desirability to patent the following forms of known

²⁴ Sometimes patent ineligibility is also used in the mix. In *Mayo v Prometheus*, the Supreme Court held a correlation between naturally-produced metabolites and therapeutic efficacy and toxicity to be an unpatentable “natural law”. Instead of determining patent ineligibility, the court could have come to the same outcome by determining a lack of inventive step. *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.* 132 S. Ct. 1289 (2012). Judge Rader argued that the language used in *Mayo* Such “should not be read to conflate principles of patent eligibility with those of validity, however. Nor should it be read to instill an “inventiveness” or “ingenuity” component into the inquiry. In *CLS Bank Int’l. v Alice Corp. Pty. Ltd.*, 717 F.3d 1269 (Fed. Cir. 2013) 99.

²⁵ The patent cliff is an informal description of the situation where a brand pharmaceutical is about to go off-patent, which will cause its revenues to nose-dive, since it will be legitimately replicated and sold by generics, at lower prices.

²⁶ “[T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” Code of Federal Regulations, Title 12, United States Food and Drug Administration.

²⁷ Carlos Correa, Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective, United Nations Development Programme (2015).

²⁸ Carlos Correa, Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective – Working Paper, ICTSD, UNCTAD and WHO (2006).

substances: claims for polymorphs,²⁹ enantiomers (optical isomers),³⁰ salts,³¹ ethers,³² esters³³, compositions,³⁴ doses,³⁵ prodrugs,³⁶ metabolites,³⁷ analogy processes,³⁸ and Markush³⁹ and selection claims.⁴⁰ To illustrate the controversy over the patentability of these (near) bioequivalent forms, three varieties will now be explored below: polymorphs, enantiomers and salts. The recurring theme will be whether the form is new or inventive and has industrial applicability. One can often observe paradoxes in intellectual property law.⁴¹ Also patent law is not immune from paradoxical questions. Does a new form of a known substance lead to the same or a different substance? Applying Mulisch' octavism doctrine to this paradox can offer some guidance: a new form of a known substance is like the music note C (for example the one with a frequency around 131 Herz) that is and is not the same C an octave higher (this is the middle C at a frequency of 262 Herz) to our ears.⁴²

²⁹ *Infra* Section 3.

³⁰ *Ibid.*

³¹ *Ibid.*

³² John Waite, *The Patentability of a Principle of Nature* (1917) 15(3) MICH. L. REV. 243.

³³ See for example *Dome Patent L.P. v Michelle K. Lee, Director, USPTO*, [Opinion] 14-1673 (Fed. Cir. 2014) 3 September 2015, available at: <http://www.cafc.uscourts.gov/sites/default/files/opinions-orders/14-1673.Opinion.9-1-2015.1.PDF>.

³⁴ See for example Thorsten Bausch, *Medeva and the Limitation of Composition Claims*, Kluwer Patent Blog, 10 October 2013, available at: <http://kluwerpatentblog.com/2013/10/10/medeva-and-the-limitation-of-composition-claims/>.

³⁵ *Infra* Section 4.

³⁶ See for example Amy Kapczynski, Chan Park, Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, PLOS One, 5 December 2012, available at: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470>.

³⁷ See for example Richard Li-dar Wang, Pei-Chen Huang, *Patent Protection of Pharmacologically Active Metabolites: Theoretical and Technological Analysis on the Jurisprudence of Four Regions* (2012) 29 SANTA CLARA HIGH TECH. L.J. 489.

³⁸ "It is well established that analogy processes are patentable insofar as they provide a novel and inventive product. This is because all the features of the analogy process can only be derived from an effect which is as yet unknown and unsuspected (problem invention)." *T 0119/82 (Gelation)*, EPO, 12 December 1983, ECLI:EP:BA:1983:T011982.19831212.

³⁹ See for example Richard Bone, *The Death of the Markush Group*, 247th American Chemical Society National Meeting Dallas TX, 20 March 2014, available at: http://www.vlplawgroup.com/pdf/ACS_Dallas2014_RichardBone.pdf. Kimberly Prior, *The USPTO's Historic Struggle with Markush Claims: Will the 2011 Guidelines Provide Relief?* (2012), Law School Student Scholarship, Paper 114, available at: http://scholarship.shu.edu/student_scholarship/114.

⁴⁰ "Novelty by selection cannot be claimed, since none of the possible combinations of all the listed starting compounds and process variants introduce a new element - indispensable for substance selection - that would result in a true and not just "identical" modification of the starting substances." *T 0012/81 (Diastereomers)* EPO, 9 February 1982, ECLI:EP:BA:1982:T001281.19820209.

⁴¹ Respectively about the paradoxes found in trademark law, geographical indications law and copyright and design rights law: Neil Wilkof, *Paradoxes and intellectual property law* (2013) 8(6) JOURNAL OF INTELLECTUAL PROPERTY & PRACTICE 423 and Michelle Agdomar, *Removing the Greek from Feta and Adding Korbel to Champagne: The Paradox of Geographical Indications in International Law*" (2008) 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 541, and Kal Raustiala and Christopher Sprigman, *The Piracy Paradox: Innovation and Intellectual Property in Fashion Design* (2006) 92 VIRGINIA LAW REVIEW 1687.

⁴² Mulisch (1927-2010) in Dutch: "De tweede toon is niet identiek met de eerste, maar ook niet niet identiek." (The second tone is not identical to the first, but also not not (*sic*) identical.) Harry Mulisch, *DE COMPOSITIE VAN DE WERELD* (Bezige Bij, Amsterdam: 1980), 113, *passim*.

Polymorphs

Polymorphism is the ability of a chemical molecule or ions to exist within different internal crystal structures. Correa argues that this is an inherent property of a substance, and therefore they are not created but discovered.⁴³ According to Correa, patents for polymorphs should be denied on the ground of absence of a patentable invention or inventive activity.⁴⁴ Correa wrote that obtaining a polymorph is a routine activity in pharmaceutical production, carried out through methods widely known to a person skilled in the art. Only a process used for the preparation of a polymorph, if novel and involving inventive step, may be patentable. The 2006 Working Draft acknowledged that different polymorphs of a drug can have substantially different functional characteristics, and that changing the polymorphic form of a drug active ingredient can result in effects such as altered bioavailability, or a change in the long-term stability profile.⁴⁵ Nevertheless Correa still argued that polymorphs are part of the prior art.⁴⁶ In contrast to this, Holman points to *Glaxo Group Ltd. v Apotex, Inc.*,⁴⁷ where the US Court of Appeals for the Federal Circuit held that the patent on the polymorph of the cefuroxime axetil⁴⁸ was valid.⁴⁹ A generic company had challenged the patent validity for obviousness since a previous patent of Glaxo⁵⁰ had disclosed the same active ingredient cefuroxime axetil in the forms of (1) an impure amorphous⁵¹ compound and (2) a purer crystalline⁵² compound. However, according to the Federal Circuit, the previous patent did not suggest that “highly pure amorphous cefuroxime axetil product would have better bioavailability and stability than a crystalline form”.⁵³ Therefore it rejected the claim of non-obviousness.

Enantiomers

Enantiomers (optical isomers) are a pair of molecules that are mirror images of each other. They share the same chemical formula. The difference resides in the three-dimensional arrangement of molecular constituents around a single carbon atom in the compounds: classified as either right- or left-handed. Chirality, when the molecule is non-superimposable on its mirror image, is relevant for most biomolecules and pharmaceuticals. Correa argued that isolated enantiomers should not be deemed patentable when the racemic mixture, which has an equal amount of left- and right-handed enantiomers of a chiral molecule, was previously disclosed.⁵⁴ According to Correa, processes for the separation and purification of enantiomers may only be patented if novel and inventive.⁵⁵ However, as Holman demonstrated, in *Forest Laboratories, Inc. v Ivax Pharmaceuticals, Inc.*,⁵⁶ the Federal Circuit held that prior art disclosing a racemic mixture did not

⁴³ Correa 2015, *supra* note 27, 9.

⁴⁴ *Ibid.*

⁴⁵ Correa 2006, *supra* note 28, 10.

⁴⁶ *Ibid.*

⁴⁷ *Glaxo Group Ltd. v Apotex, Inc.*, 376 F.3d 1339, 1342-43 (Fed. Cir. 2004)

⁴⁸ U.S. Patent Number 4,562,181.

⁴⁹ Christopher Holman, In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination, (September 2, 2016), Indiana Law Review, Forthcoming, available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2833983.

⁵⁰ U.S. Patent Number 4,267,320.

⁵¹ Amorphous = randomly distributed.

⁵² Crystallize = regularly recurring pattern.

⁵³ *Glaxo Group Ltd.*, *supra* note 46, D2 para 3.

⁵⁴ Correa 2015, *supra* note 27, 10.

⁵⁵ *Ibid.*

⁵⁶ *Forest Laboratories, Inc. v Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007).

render a purified enantiomer obvious. Instead, the court found that attempting to separate the enantiomers of citalopram based on the knowledge of one of ordinary skill in the art would have required undue experimentation. The court held that the Smith reference, despite of referring to the racemic mixture which included a purified enantiomer, as claimed by Ivax, was not enabled and was therefore not part of the prior art. Ivax also failed to prove that the patent was obvious. Instead, the court held that the person skilled in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate.⁵⁷

Salts

About half the molecules used in medicinal therapy are administered as salts.⁵⁸ Bansal, Kumar and Amin explain that salification of a drug substance can overcome the suboptimal biopharmaceutical or physicochemical properties by pairing it to a counterion.⁵⁹ According to Correa the preparation of salts with advantageous properties over the drug in its free base/acid form is part of the common knowledge of a person skilled in the art⁶⁰ and are therefore deemed obvious. In contrast to Correa, Holman pointed to *Pfizer v Apotex* in 2007,⁶¹ where Federal Circuit Judge Newman in her dissent to the majority decision observed that “[b]oth sides acknowledge that the effects of chemical changes on properties of medicinal products is [*sic*] not predictable”.⁶²

Section 3(d) Patents Act of India, states that only new forms of known substances that enhance efficacy are patentable.⁶³ In *Novartis AG v Union of India*,⁶⁴ the Supreme Court of India held that the efficacy of beta crystalline form of Imatinib mesylate should be tested depending on the function, utility, or the purpose of the product under consideration. Thus for a medicine, the test should be therapeutic efficacy, which should be construed strictly and narrowly. The physico-chemical properties of beta crystalline form of Imatinib mesylate: better thermodynamic stability and lower hygroscopicity,⁶⁵ “may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of Section 3(d), since these properties have nothing to do with therapeutic efficacy.”⁶⁶ Increased bioavailability alone may not necessarily lead to an enhancement of therapeutic efficacy, as Khader points out: it should have been specifically claimed and established by research data.⁶⁷

⁵⁷ *Ibid.*

⁵⁸ And just as with other patent claims, novelty, non-obviousness and industrial application are requirements. In *Pfizer Inc. v Apotex, Inc.*, the CAFC held that the claims 1-3 for the US Patent No. 4,879,303, entitled “Pharmaceutically Acceptable Salts” were obvious. *Pfizer Inc. v Apotex, Inc.* 480 F.3d 1348 (Fed. Cir. 2006) paragraph 80.

⁵⁹ Arvind Bansal, Lokesh Kumar, Aeshna Amin, Salt Selection in Drug Development (2 March 2008) 32(3) PHARMACEUTICAL TECHNOLOGY, available at: <http://www.pharmtech.com/salt-selection-drug-development>.

⁶⁰ Correa 2015, *supra* note 28, 9.

⁶¹ “[T]he prior art salts of amlodipine were plagued by a number of undesirable properties that stood in the way of creating an optimized product, such as stickiness, instability, low solubility and hygroscopicity, but these deficiencies were unexpectedly solved by development of the besylate salt of the drug.” Holman, *supra* note 49, 21.

⁶² *Pfizer, Inc. v Apotex, Inc.*, 488 F.3d 1377, 1379 (Fed. Cir. 2007)(Newman dissent).

⁶³ Khader, *supra* note 22, 96.

⁶⁴ *Novartis AG v Union of India* AIR 2013 SC 1311, 2013 (54) PTC 1(SC), (2013) 6 SCC 1.

⁶⁵ The hygroscopicity of a salt is that they readily dissolve in the water they absorb.

⁶⁶ *Novartis AG*, *supra* note 64.

⁶⁷ Khader, *supra* note 22, 100.

Section 4. The dose makes the medicine and stratified medicines

The alchemist Paracelsus is credited for the adage that “the dose makes the poison”.⁶⁸ In the same vein, the right dose of a medicine has the most curative properties. Also, the right kind of patient will be optimally healed by a certain medicine. This raises questions whether a new dosage for a known substance, or a specific patient group for a known substance meets the standard of patentability. Does it lead to a difference in degree or in kind? Will a person skilled in the art anticipate the result or is it obvious?

Dosage

The U.S. Government Accountability Office criticized “[t]he practice commonly known as producing line extensions – deriving new products from existing compounds by making small changes to existing products, such as changing a drug’s dosage”.⁶⁹ Correa argued that claims over the dose of a drug fail to comply with the industrial applicability requirement.⁷⁰ Correa reasons that dosage claims should be qualified, in spite of their appearance, as a composition (or combination) claim. And since these combinations of known drugs are considered methods of treatment, they lack industrial applicability. Holman does not concur, since “a claim to a drug dose is no more equivalent to a method of using the drug than a claim to a novel active ingredient is equivalent to a claim to a method of using the active ingredient.”⁷¹ Holman pointed to Allergan, which had developed Lumigan, whose original formulation, contained 0.03 percent of the active ingredient bimatoprost and 50 parts per million benzalkonium chloride.⁷² The latter is a preservative that inhibits bacterial growth in ophthalmic solutions, but it can also damage the cells on the ocular surface. Allergan invested in research to reduce the negative side effects while maintaining therapeutic efficacy. This was achieved by reducing the dosage of the active ingredient in conjunction with an increased concentration of benzalkonium chloride. In *Allergan, Inc. v Sandoz Inc.*,⁷³ the Federal Circuit held that the claimed formulation by Allergan exhibited “unexpected results,” which differed from the prior art. It meant “the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment”⁷⁴.

Sanofi-Aventis Deutschland GmbH v Glenmark Pharmaceuticals Inc.,⁷⁵ makes clear that a reduction of dosages can lead to great improvements. Tarka is the patented combination antihypertension medicine that consists of the angiotensin converting enzyme inhibitor trandolapril and the calcium channel blocker verapamil hydrochloride and can be administered in a single dosage. Alternatives such as enalapril and captopril needed to be dosed, respectively two and three times per day.⁷⁶ This multiple dosages cause multiple imbalances in the human body and

⁶⁸ The Latin adage *Sola dosis facit venenum* was credited to Theophrastus Philippus Aureolus Bombastus von Hohenheim, also known as Paracelsus (1493-1541).

⁶⁹ Government Accountability Office, New Drug Development. Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, Washington D.C, 2006, 34.

⁷⁰ Correa 2015, *supra* note 27, 10.

⁷¹ Holman, *supra* note 49, 40.

⁷² Holman, *supra* note 49, 25, 26 and 40.

⁷³ *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015).

⁷⁴ *Ibid.*

⁷⁵ *Sanofi-Aventis Deutschland GmbH v Glenmark Pharm. Inc.*, USA, 748 F.3d 1354, 1356 (Fed. Cir.), cert. denied, 135 S. Ct. 759 (2014).

⁷⁶ Response Brief of Plaintiffs-Appellees, *Sanofi-Aventis Deutschland v Glenmark Pharmaceuticals, Inc.*, 2012 WL 5928463 at 12 (Fed. Cir.).

compliance problems.⁷⁷ In other words dosages might lead not only to a difference in degree but also to a difference in kind in comparison to the prior art.

Stratified medicines

Because of genetic variations or other variations, people will respond differently to medicines⁷⁸ and/or how these medicines are administered. Towards the end of a patent life-cycle, pharmaceutical companies will be stimulated to classify patients into groups that are most susceptible for a pharmaceutical or medical intervention if certain biomarkers or combination of biomarkers are determined via diagnostic tests.⁷⁹ To patent the claims for known substances and new medical use or diagnostics for stratified medicine⁸⁰ objections of non-patentability and non-novelty need to be overcome.⁸¹

Non-patentability

The court in *Mayo Collaborative Services v Prometheus Laboratories, Inc.*,⁸² clarified that although, method of treatment claims are patentable subject matter in the U.S., the relationship between thiopurine metabolite and the efficacy of the drug is a “law of nature” and therefore excluded from patentability.⁸³ Following *Prometheus*, the Court of Appeals for the Federal Circuit revisited this decision in the case *Association for Molecular Pathology v Myriad Genetics, Inc.*⁸⁴ In that proceeding, the Federal Circuit maintained its decision that the method claims with steps that involved “analyzing” sequences and “comparing” them were not patent eligible, but the method for screening potential cancer therapeutics was patent eligible as it involved growing transformed cells and determining the rate of growth of those cells.

⁷⁷ Non-compliance with drug therapy is a serious problem to society which can lead to superbugs resistant to antibiotics. See Antimicrobial resistance, factsheet, WHO, September 2016, available at: <http://www.who.int/mediacentre/factsheets/fs194/en/>.

⁷⁸ Herceptin (trastuzumab) was not considered to be cost-effective by the Scottish Medicines Consortium and National Institute of Health and Clinical Excellence in the large gastric cancer population. However, the medicine got a second chance once the companion diagnostics could define HER2 overexpression subgroup in which had much better results. Ildar Akhmetov and Rostyslav Bubnov, Assessing value of innovative molecular diagnostic tests in the concept of predictive, preventive, and personalized medicine, 6(19) EPMA J. 2015, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588236/>. See also, THE CASE FOR PERSONALIZED MEDICINE, 4th edition, Personalized Medicine Coalition, 2014, 9.

⁷⁹ Robert Bohrer, Personalized medicines update, Pharmaceuticals Policy, 5 November 2015, available at: <http://pharmaceuticalpolicy.blogspot.hk/2014/11/personalized-medicine-update.html#more>.

⁸⁰ Courtenay Brinckerhoff, New USPTO Guidance On Patent Eligibility Of Diagnostic Methods, Pharma Patents Blog, 9 May 2016, available at: <https://www.pharmapatentsblog.com/2016/05/09/new-uspto-guidance-on-patent-eligibility-of-diagnostic-methods/>.

⁸¹ Obviously, the goal of stratified medicine is to provide “the right treatment to the right patients at the right time”. See Michael Rugnetta and Whitney Kramer, Paving the Way for Personalized Medicine, Science Progress, September 2009, 3, available at: https://www.scienceprogress.org/wp-content/uploads/2009/09/personalized_medicine.pdf.

⁸² *Mayo Collaborative Services, v Prometheus Laboratories, Inc.*, *supra* note 24, 1293.

⁸³ 35 U.S.C. § 101. “The LabCorp dissent voices many of the concerns raised by critics of the patent system, arguing that too much patent protection can impede rather than promote progress in science and technology, and attributing an important role to patent eligibility as a gatekeeper to guard against such overprotection.” Holman referring to *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.* 548 U.S. 124 (2006). Christopher Holman, Patent Eligibility as a Policy Lever to Regulate the Patenting of Personalized Medicine (February 18, 2015), in PERSPECTIVES ON PATENTABLE SUBJECT MATTER, edited by Michael Abramowicz, F. Scott Kieff and James E. Daily (Cambridge University Press, 2014), available at: <https://ssrn.com/abstract=2566924>.

⁸⁴ *Myriad Genetics*, *supra* note 8.

Non-novelty

Inherent anticipation should be considered when claiming a method of treatment involving administering a known drug for a known therapeutic purpose based on a previously unknown correlation with a biomarker or group of biomarkers. However, certain factors increase the chance that diagnostics claims are patentable. For example the detection of one of the aforementioned near bioequivalent markers, such as a single nucleotide polymorphism, or adding an active treatment-type step. The claims for diagnostics can have several forms including: a method to determine whether patient with disease X will be responsive to drug Z, comprising detecting biomarker Y and predicting efficacy with Z if Y is present. Citing actual boundaries on the compound administered; the method of administration and dosage can help increase the chances that the claims are accepted by the patent office.⁸⁵

5. Conclusions

Pharmaceutical companies standing on the patent cliff staring in the abyss devoid of future income, become very inventive in finding new medical uses for the known substance, which modestly, by a process of sometimes capricious tinkering with the claim descriptions and sometimes evolutionary refinements, can raise the state of the art. This, again, could evoke Borges' poem *The Alchemist*:

“He knows that gold, that Proteus, is lurking
in all chance happenings, like destiny;
he knows it hides in the dust along the way,
in the action of the bow, the arm, the arrow.”⁸⁶

Just as the medieval alchemists were not only potterers and bunglers, but, as recent research discovered, in fact *proto*-scientists,⁸⁷ the originator pharmaceutical companies develop a perpetual series of therapeutic and diagnostics patents, based on efficacy studies, which can have real benefits to the quality of patients' lives. For this reason the Hong Kong government facilitates the legal fiction that first and further medical use claims differentiate from methods of medical treatment and recognizes them as patent-eligible under certain conditions. Another argument for granting patents to these medical use claims is the Lockean “sweat of the brow” rationale: often these incremental innovations only materialize after huge investments.

Governments that are responsible for balancing the interests of patent right holders and the public at large have to take into account what the influence is of relaxing or ignoring the novelty or inventiveness requirements. The slackening of patent standards, which facilitates second and further medical use patents, could stifle generic pharmaceutical companies from manufacturing

⁸⁵ Duane Marks, *Diagnostic Method Patents, A Framework for Patent-Eligibility of Diagnostic Method Patents* post-Mayo, March 20, 2014, available at: https://www.uspto.gov/sites/default/files/patents/announce/may9forum_marks.pdf

⁸⁶ Jorge Luis Borges, *supra* note 1, paragraph 2.

⁸⁷ “What intrigues Principe and his fellow historians, though, is the growing evidence that the alchemists seem to have performed legitimate experiments, manipulated and analyzed the material world in interesting ways and reported genuine results. And many of the great names in the canon of modern science took note, says William Newman, a historian at Indiana University Bloomington.” Richard Conniff, ‘Alchemy May Not Have Been the Pseudoscience We All Thought It Was’, *Smithsonian*, February 2014, available at: <http://www.smithsonianmag.com/science-nature/alchemy-may-not-been-pseudoscience-we-thought-it-was-180949430/#iwZgyYdHqXP3WziY.99>.

generic medicines and withhold the public from affordable medicines. Hong Kong has neither a substantial originator nor a generics pharmaceutical industry. It wants to be perceived as a trusted member of the international legal community. Thus it presents itself in the amended patent bill as a staunch protector of intellectual property rights by allowing second and further medical use claims to be patented. However, this decision could only be justified if it also guarantees that only those inventions will be granted a patent if they can prove heightened efficacy or proof that they have the utility as they promised in the claims. One can argue that both these requirements are TRIPS compatible and make use of the flexibilities of for example Article 8 of this treaty.⁸⁸ In India, a country with an important generics pharmaceutical industry, Section 3(d) Patents Act describes that new forms of known substances can be granted if an enhanced efficacy can be proved by the patent applicant.⁸⁹ In Canada, the doctrine of promised utility ascended. The Court of Appeal in *Eli Lilly Canada Inc. v Novopharm Ltd.*⁹⁰ held that the patent for Olanzapin was invalid as the promised utility that was claimed had not been demonstrated and could not have been soundly predicted. Merges points to the drawback of this approach: the required proof of utility at the filing date deters necessary investment because it delays the award of an exclusive right until a significant amount of money has been spent.⁹¹

Both aforementioned Indian and Canadian standard enhancers are worth considering for the Hong Kong policy makers. Especially, since they also solve the asymmetric knowledge relation between patent holders and patent office. Without such complementary guarantees, the scales could be tipped in the Hong Kong patent system towards protection of extending originators' interests, while Hong Kong's patients would miss out on affordable medicines. And of course, the Hong Kong courts, also taking the public interest into account, could decide to vary the protection of patent claims according to the level of inventiveness.

⁸⁸ Article 8(1) TRIPS: "Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement."

⁸⁹ Khader, *supra* note 22, 96.

⁹⁰ *Eli Lilly Canada Inc. v Novopharm Ltd.*, 2012 FCA 232.

⁹¹ See Robert Merges, Expert Report in the Arbitration under the Arbitration Rules of the United Nations Commission on International Trade Law and the NAFTA (Case No. UNCT/14/2), *Eli Lilly and Company v Government of Canada*, 29 September 2014, available at: <http://www.italaw.com/sites/default/files/case-documents/italaw4141.pdf>.

"Firms that seek venture-funding appear to be patenting more actively prior to the funding event (and for the purpose of securing funding), and venture-capital investors appear much less willing to fund companies that hold no patents." Stuart J.H. Graham, Robert P. Merges, Pamela Samuelson, and Ted Sichelman, High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey (2009) 24 BERKELEY TECH. L.J. 1255, 1280.