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Pharmaceutical Patent Protection and Section 3(D): *A Comparative Look at India and the U.S.*

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ABSTRACT

India is an important emerging market for the pharmaceutical industry, with a large population, significant unmet medical need, and a growing middle class representing a large potential pool of consumers for innovative medicines. Nestled within India's statutory patent regime is a provision governing patenting of new forms of known drug substances that is unique among member countries to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). This paper advances the idea that the provision known as Section 3(d) is ambiguously drafted and provides insufficient advance guidance to innovators. This paper will discuss relevant Indian case law, as well as associated implications for pharmaceutical innovator companies. Also presented is a comparative analysis of the historical treatment of Section 3(d)-type issues under U.S. law and discussion about possible future developments in non-obviousness jurisprudence related to pharmaceutical forms in the post-KSR world.

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I. INTRODUCTION

India is an important emerging market for the pharmaceutical industry, its large population, significant unmet medical need, and growing middle class forming a large potential pool of consumers for innovative medicines and medical treatments. Despite the well-established presence of a home-grown generic drug industry, pharmaceutical innovator companies continue to increase their presence in India, a country with a rapidly growing economy and a large, technologically savvy workforce.

At the same time, Indian patent law has evolved dramatically, particularly in light of India's accession to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Indian patent law has undergone multiple transformations during the last decade in an attempt to comply with TRIPS. Nestled within India's statutory patent regime is a provision unique among TRIPS countries governing patenting of new forms of known substances. This provision raises a substantial statutory bar to patenting new salts or polymorphs of known pharmaceutical substances, and was apparently intended by the Indian Parliament to reign in the practice known as "evergreening" by pharmaceutical innovator companies.[1] This paper advances the idea that this provision, known as Section 3(d),[2] is ambiguously drafted and provides insufficient advance guidance to those seeking pharmaceutical patent protection in India as to which incremental improvements to the art are patentable and which are not.

The Indian High Court's recent construction of Section 3(d) in *Novartis AG v. Union of India*[3] raises serious concerns about where the patentability line will be drawn in the future for pharmaceuticals under the Indian Patent Act. The Court's surprising treatment of Section 3(d) in *Novartis* appears to have broad implications for innovator companies seeking patent protection for new polymorphic, enantiomeric or salt forms of known chemical entities. The High Court's failure to define a clear and quantitative standard for the efficacy improvement required to meet the 3(d) threshold leaves substantial legal uncertainty around when new forms of known chemical entities will be patentable, regardless of their value to society in terms of increased pharmacological activity or other improvements in pharmaceutical properties. This uncertainty could certainly stifle investment in many of the incremental improvements that would advance the arsenal of beneficial drug treatments over time. Further, while the patentability threshold for incremental improvements in the United States remains less harsh than in India, the winds of change are clearly blowing following the U.S. Supreme Court's *KSR v. Teleflex*[4] decision. The courts and patent examiners have significantly more leeway after *KSR* in determining the patentability (or conversely, the obviousness) of incremental inventions.

The approach of speed-to-market with a new drug followed by one or more incremental improvements has historically been a very important strategic paradigm for maximizing return on research investment by innovator companies. As such, the *Novartis* decision may require a re-evaluation of the current business model for such companies in managing the life cycles of their products. Some new drugs may simply never get developed at all if removal of patent protection for incremental improvements tips the cost-benefit analysis for a particular new product away from an adequate long-term return on investment. The current business model creates built-in incentives to invest in post-approval improvements to new drugs, including the types of improvements precluded by the constraints in Section 3(d). At the same time, Section 3(d) and the *Novartis* decision create innovation disincentives that may ultimately undermine some of

[1] *Novartis Patent Challenge Dismissed in India*, INT'L CTR. FOR TRADE AND SUSTAINABLE DEV. (Sept. 5, 2007), http://ictsd.org/i/news/bridgesweekly/7819/.

[2] The Patents (Amendment) Act, 2005, No. 15, Acts of Parliament, 2005.

[3] Novartis AG v. Adarsh Pharma., 2004 (29) P.T.C. 108 (Mad.).

[4] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 401 (2007).

the very protections intended by TRIPS to ensure a truly global marketplace for scientific developments, particularly if other countries follow suit.

This paper will discuss Section 3(d), relevant Indian case law, and associated implications for pharmaceutical innovator companies doing business in India. It will also present a comparative analysis of the historical treatment of Section 3(d)-type issues under U.S. law, as well as a discussion about possible future developments in non-obviousness jurisprudence related to pharmaceutical forms in the United States in the post-*KSR* world. As discussed above, the trend represented by *KSR* threatens to undermine some of the fundamental tenets of TRIPS if individual nation states continue adopting rulings like *KSR* and *Novartis*, limiting patentees' rights to protection for incremental improvements to their inventions.

II. BACKGROUND

A. Patent Related Obligations of Countries Subscribing to TRIPS

1. History and overview of TRIPS as it applies to patents

The World Trade Organization (WTO) has harmonized international minimum standards for the protection of intellectual property rights through the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).[5] TRIPS became effective on January 1, 1995 by agreement of WTO member states,[6] who then became obligated to implement domestic laws to comply with the TRIPS minimum requirements. Developing countries were initially given up to five years (i.e. until January 1, 2000) to implement domestic laws in accordance with TRIPS.[7] Member states obligated to provide patent protection for an area of technology for which no domestic protection existed as of the effective date of TRIPS received an additional five years (for a total of ten years, or until January 1, 2005) to bring their domestic laws into complete compliance with respect to product patents in the new area of technology.[8] Examples of such previously unpatentable areas of technology includ final dosage forms of drugs (i.e. drug product formulations such as immediate or extended release tablets, injectable solutions, etc.), which were unpatentable under the 1970 Patents Act.[9] Both of these five-year provisions applied to India in the area of pharmaceuticals, as both a developing country and as a country whose laws as of the date TRIPS became effective made no provision for patent protection of drug products.[10] Pre-TRIPS patent provisions governing pharmaceuticals will be discussed in more detail below.

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[5] Agreement on Trade-Related Aspects of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Apr. 15, 1994, 1869 U.N.T.S. 299, 33 I.L.M. 1197. [hereinafter TRIPS Agreements].

[6] As of July 2008, 153 countries were member states in the WTO. In addition to the United States, Canada, and the European Union, the list includes many developed and developing countries in Asia, Africa, Central and South America, and the Middle East (e.g. China, India, Brazil, Rwanda, and UAE). *Understanding the WTO: The Organization Members and Observers*, WORLD TRADE ORGANIZATION, http://www.wto.org/english/theWTO_e/whatis_e/tif_e/org6_e.htm (last visited Oct. 26, 2010).

[7] TRIPS Agreements, *supra* note 7, art. 65.1–2.

[8] *Id*. art. 65.4.

[9] The Patents Act, 1970, No. 39, Acts of Parliament, 1970 at 5(1)(a) [hereinafter The 1970 Act].

[10] *Id.*

Patent protection must be available for both products and processes under TRIPS Article 27.1.[11] Such protection is available to products or processes in any field of technology provided that the product or process is "new, involve[s] an inventive step and [is] capable of industrial application."[12] Patent rights must include the right to exclude others from "making, using, offering for sale, selling, or importing" the patented product without authorization.[13] Patent rights must extend for a minimum of twenty years from the date of filing under the agreement.[14] Under TRIPS, member states must require inventors to disclose the invention in sufficient detail to enable a skilled artisan to carry out the invention.[15] Further, member states may, at their discretio n, require inventors to disclose the best mode of practicing the invention as known to the inventor as of the filing date.[16]

Member states are given substantial flexibility in denying patents on otherwise patentable inventions when "necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the [commercial] exploitation is prohibited by their law."[17] In other words, it is possible for member states to establish rules limiting patent rights in certain specific circumstances (e.g. public health emergencies), but it is not permissible to establish blanket laws declaring the commercial exploitation of an entire class of invention impermissible. The ambiguity in the text of the TRIPS in defining key requirements for patentability notably leaves substantial room for interpretation by individual member states:

> When the vital constituents of patentability[,] i[.]e[.] 'novelty', 'inventive step' and 'industrial application' were left undefined in the TRIPS, it was almost certain that member countries of the WTO would take liberties in defining them. One instance of the exercise of such liberty is . . . [the Indian] definition of 'inventive step' in section 2(1)(ja) which adds 'technical advancement' and 'economic significance' over and above the classic requirement of 'obviousness to a person skilled in the art'. Neither do[es] the open list of exceptions to patentability in the TRIPS Agreement help in defining the standard.[18]

2. Interpretation of TRIPS Obligations and the Doha Declaration

Subsequent to the adoption of TRIPS, many countries in the developing world expressed concerns about applying its patent provisions to human pharmaceuticals, particularly as related to affordable treatments for public health crises, such as the AIDS epidemic in sub-Saharan Africa. Given the vital role of medicines in human well-being, objecting countries sought to relax the scope of patent protections required for

[11] TRIPS Agreements, *supra* note 7, art. 27.1.
[12] *Id*.
[13] *Id*. art. 28.1.
[14] *Id*. art. 33.
[15] *Id*. art. 29.1.
[16] *Id*.
[17] *Id*. art. 27.2.
[18] Feroz Ali, *Silences in the TRIPS Agreement*, PHARMA PATENTS, (Aug. 25, 2007, 6:25 AM), http://pharmapatents.blogspot.com/2007_08_01_archive.html.

pharmaceuticals. Both developed countries, such as the United States and Switzerland, and pharmaceutical industry trade groups disputed the notion that patent protection for drugs was a key factor in limiting access to medications in developing countries.

These divergent viewpoints came together at the Doha meeting held in Doha, Qatar in November 2001, a meeting at which a coalition of developing nations "sought a legally binding declaration that would affirm an interpretation of TRIPS that would permit them to pursue policies affording access to essential medicines without fear of retribution from other WTO members."[19] The Doha Declaration, as adopted on November 14, 2001, contained the following provision: "[w]e agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health."[20] The net effect of the Doha Declaration was to affirm at least some of the flexibility sought by the coalition in interpreting and implementing intellectual property provisions of TRIPS. This effect is quite evident in the following passage from the Declaration: ". . . we affirm that the [TRIPS] Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all."[21]

B. Evolution of Pharmaceutical Patent Protection in India

1. Historical overview

Anti-patent sentiments, particularly related to medicines and health, may be more common in Indian cultural tradition than in Western societies. The perspective of a limited role for legal intellectual property protections for medicines is illustrated by a comment made by Prime Minister Indira Gandhi during a speech before the World Health Assembly in 1982: "[t]he idea of a better-ordered world is one in which medical discoveries will be free of patents and there will be no profiteering for life and death."[22] Consistent with this view of intellectual property rights is the practice of free-riding, or "disregarding a foreign patent and manufacturing the product that the patent protects."[23]

> Of course, since patents are territorial, some countries may decide that they can win by free-riding on the patented technology developed elsewhere without substantially slowing the march of technological development. In this way, their societies are advantaged, although if everybody adopted this strategy, societies worldwide would lose out as technological advancement slowed. Moreover, this strategy is more likely to be followed in the more socialized areas of a country's economy. Thus, many countries have in the past adopted weak patent protection for

[19] Susan K. Sell, *TRIPS and the Access to Medicines Campaign*, 20 WIS. INT'L L.J. 481, 516 (2002).

[20] World Trade Organization, Ministerial Declaration on the TRIPS Agreement and Public Health, WT/MIN(01)/ DEC/2, 41 I.L.M. 746 (2001), *available at* http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.

[21] *Id*.

[22] Indira Gandhi, Address Before the World Health Assembly, Geneva (May 1982), *in* INTELLECTUAL PROPERTY RIGHTS: GLOBAL CONSENSUS, GLOBAL CONFLICT? 186 (R. Michael Gadbaw & Timothy J. Richards eds., 1988).

[23] Stephen Barnes, Comment, *Pharmaceutical Patents and TRIPS: A Comparison of India and South Africa*, 91 KY. L.J. 911, 919 (2003).

> pharmaceuticals, an industry whose structure makes it particularly dependent on the existence of a patent system. They let the rest of the world, particularly the wealthy Western countries, pay the cost of the development of new drugs and hope that the failure to participate will not stunt so many drugs' development that the strategy backfires. One surprising former member of this club is Canada. India is one of the most important current members. Indeed, India is a good example of what can happen when a large percentage of the world's population decides to go its own way, and part of its strategy is to place the cost of developing new drugs on others.[24]

An important result of the free-riding practice has been the development in India of a very strong generic pharmaceutical industry. This highly competitive industry uses reverse-engineering to copy patented drugs and produce them at a very low cost.[25] The development of a thriving generic industry in India in recent decades is at least in part "a direct result of highly protectionist Indian patent law."[26]

Under British colonialism, Indian patent laws were based on British law. The Indian Patents and Designs Act of 1911, which provided for a fourteen year patent protection term from the date of filing, formed the basis of Indian patent law.[27] An amendment to the Act in 1930 extended the term of protection from fourteen to sixteen years.[28] Under the system established by the 1911 Act, eighty to ninety percent of India's patents came to be held by foreigners.[29] Further,

> [i]n the early 1940s and 1950s, ninety percent of the [Indian] drug market was under the control of foreign companies, and the country was totally dependent on imports for both bulk drugs (the active ingredients) and formulations (the medicines made from bulk drugs). As a result, Indian drug prices were then among the highest in the world.[30]

Following independence from Britain in 1947, two government committees, the Tek Chand Committee in 1948 and the Ayyangar Committee in 1957 were formed to study India's patent regime and to recommend improvements to "make . . . [the system] more Indian and more in line with national goals."[31] The committees reached the determination that "India's patent system was allowing foreigners to 'achieve monopolistic control over the market' in major industries such as food, chemicals and pharmaceuticals."[32] As a result of this work, and following a long period of debate and

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[24] Martin J. Adelman & Sonia Baldia, *Prospects and Limits of the Patent Provision in the TRIPS Agreement: The Case of India*, 29 VAND. J. TRANSNAT'L L. 507, 510–11 (1996).
[25] Barnes, *supra* note 25, at 919.
[26] Johanna Sheehe, *Indian Patent Law: Walking the Line?*, 29 NW. J. INT'L L. & BUS. 577, 580 (2009).
[27] The Indian Patents and Designs Act, 1911, No. 2, Acts of Parliament, 1911.
[28] The Indian Patents and Designs Act, 1911, No. 2, Acts of Parliament, 1911, (amended 1930).
[29] Barnes, *supra* note 25, at 920.
[30] *Id.*
[31] *Id.*
[32] Sheehe, *supra* note 28, at 580–81.

delays, the Indian Patent Act of 1970 was passed by the Indian Parliament in September 1970.[33]

2. Indian Patent Act of 1970

The Indian Patent Act of 1970 severely restricted the availability of patent protection for food and drug products. Most inventions enjoyed a patent term of fourteen years,[34] with the exception of methods or processes for the manufacture of substances intended for use as a food or a drug, in which case the patent term was limited to five years from the date of issue of the patent, or seven years from the date of application, whichever came first.[35]

Even more striking about the 1970 Act is that patent protection for drug products was completely unavailable.[36] Only the process or method of making the drug product could be patented, and then only on the limited basis described above. This limitation opened the door very widely for the development of synthetic "work-arounds" or alternative synthetic routes for successful drugs, effectively allowing generic houses in India to ignore process patents held by drug innovator companies.

The 1970 Act appears to have been aimed at protecting the domestic supply of medicines and the associated independence from foreign drug manufacturers. Policy goals outlined in the text of the Act itself includes the following:

> that patents are granted to encourage inventions and to secure that the inventions are worked in India on a commercial scale [i.e. that the inventions are fully exploited by being made consistently available for sale and/or use at a reasonable commercial scale] and to the fullest extent reasonably practicable without undue delay.[37]

The Act further states "that [patents] are not granted merely to enable patentees to enjoy a monopoly for the importation of the patented article,"[38] signaling a clear policy of favoring domestic manufacturers over extensive importation by foreign companies.

Such dramatic changes in the pharmaceutical patent landscape helped tip the industry balance away from foreign players toward a strong domestic drug industry. By 1996, an estimated seventy percent of India's requirements for bulk drugs and ninety percent of its requirements for formulated drugs were met by domestic drug manufacturers.[39]

C. TRIPS and the Indian Patents (Amendment) Act of 2005

Joining the WTO in 1995 meant that India was required to bring its laws up to full compliance with TRIPS standards within the ten year grace period granted to developing countries. The TRIPS agreement also imposed additional interim

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[33] *Id.*
[34] The 1970 Act, *supra* note 11, at § 53(1)(b).
[35] *Id.* § 53(1)(a).
[36] *Id.* § 5(a).
[37] *Id.* § 83(a).
[38] *Id.* § 83(b).
[39] Adelman & Baldia, *supra* note 19, at 527.

requirements on member states with respect to pharmaceuticals and agricultural chemicals. Specifically, Article 70.8 required the establishment of a secure process for filing and establishing the priority of pharmaceutical patent applications during the transitional period.[40] The interim filing process was popularly known as the "mailbox" approach, an administrative process for the orderly receipt and date stamping of new applications until the country's laws could "catch up" to TRIPS requirements, at which time the mailbox applications could be processed according to their priority receipt date. Article 70 also required transitional members to grant exclusive marketing rights for pharmaceuticals for which a patent and marketing approval had been obtained previously in another member state and on which a patent application was filed in that transitional member state. Such exclusive marketing rights must be granted by the transitional member "for a period of five years after obtaining marketing approval in that Member [state] or until a product patent is granted or rejected in that Member [state], whichever period is shorter."[41]

In 1996 and 1997, both the United States and the European Union brought complaints before the WTO[42] alleging that India had "failed to implement both a legally sufficient 'mailbox system' within the meaning of TRIPS Article 70.8, and system of exclusive marketing rights under Article 70.9."[43] The WTO review panel agreed with the complainants, holding that India's "mailbox system" did not provide a secure means by which patent applications could be filed, and that India violated Article 70.9 by failing to provide a mechanism for exclusive marketing rights to patent applicants between the filing and granting (or denial) of a patent.[44] India appealed the decision, which was affirmed by the appellate body.[45] To comply with the order, the Indian Parliament reluctantly passed the Patents (Amendment) Act of 1999,[46] made retroactive to January 1, 1995.[47]

In 2005, the Indian Patents Act of 1970 was further amended to presumptively bring it into full compliance with TRIPS prior to the ten-year deadline.[48] Particularly controversial were the revisions made to Section 3(d) of the Act, part of a section addressing unpatentable subject matter. Specifically, the revised section provides the following:

> The following are not inventions within the meaning of this Act . . . (d) the mere discovery of a new form of a known substance . . . or the mere discovery of any new property or new use for a known substance or of the

[40] TRIPS Agreements, *supra* note 7, art. 70.8 (a)–(c).

[41] *Id.* art. 70.9.

[42] Panel Report, *India-Patent Protection for Pharmaceutical and Agricultural Chemical Products*, WT/DS50/R (Sept. 5, 1997).

[43] Sheehe, *supra* note 28, at 582.

[44] *Id.*

[45] Appellate Body Report, *India-Patent Protection for Pharmaceutical and Agricultural Chemical Products*, WT/DS50/7 (Dec. 19, 1997).

[46] The Patents (Amendment) Act, 1999, No. 17, Acts of Parliament, 1999 [hereinafter 1999 Amendment].

[47] *Id*.

[48] The Patents (Amendment) Act, 2005, No. 15, Acts of Parliament, 2005 [hereinafter 2005 Amendment].

> 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.[49]

The revised section goes on to offer further explanatory comments on the contours of a "known substance" as follows:

> *Explanation* : For the purposes of this clause, 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[.][50]

However, what the text of the section and the explanatory comments fail to provide is a useful definition for "efficacy" or what constitutes a sufficient enhancement of efficacy to meet the standard.[51] The revised section therefore leaves substantial questions about what constitutes sufficient improvements in a drug to qualify as a substantial increase in efficacy. Are enhanced pharmacological effects through increased bioavailability enough? Would submission of data to show a substantial improvement in physicochemical properties constitute a sufficient improvement in efficacy to warrant patent protection? Nothing in the body of the statute clarifies what is meant by "efficacy" or what the threshold for a sufficient increase in efficacy is for purposes of establishing patentability.

Aside from the ambiguity and legal indefiniteness in the revised section, Section 3(d) sets an unusually high obviousness hurdle for the patenting of new drug forms. It is worth noting the significant substantive differences between the revised section (shown above) and the original text of Section 3(d):

> The following are not inventions within the meaning of this Act . . . (d) 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.[52]

The original text of the 1970 Act[53] does not distinguish new physical or salt forms of known chemical entities for special (negative) treatment, as does the 2005 revision of Section 3(d).[54]

The 2005 Amendment also makes allowances for both pre- and post-grant opposition to patent applications by third parties.[55] Pre-grant opposition can be advanced on a number of grounds, including fraud and an assertion that the invention "as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, . . . having regard to what was used in India before the priority date of the

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[49] *Id.* § 3(d).
[50] *Id.*
[51] Sheehe, *supra* note 28, at 584.
[52] The 1970 Act, *supra* note 11, § 3(d).
[53] *Id.*
[54] 2005 Amendment, *supra* note 50, § 3(d).
[55] *Id.* § 25.

applicant's claim."[56] Post-grant opposition may be filed within one year of the date of publication of the patent's grant. Obviousness and lack of inventive step are also sufficient grounds for a post-grant challenge to the validity of the issued patent.[57] The statute provides for creation of special bodies known as Opposition Boards, charged with reviewing post-grant opposition documents and making a recommendation to the Patent Controller on the validity of the challenged patent.[58]

D. The Emerging Indian Pharmaceutical Market

The current Indian population of 1.1 billion is expected to grow to 1.4 billion by the year 2020.[59] The current population "includes a rapidly growing middle class of about 300 million."[60] Of those, it is estimated that approximately one-third, or 100 million, "can afford [access to] quality private health care."[61] This sub-population certainly represents an attractive target market for new drugs and other medical innovations, whether invented abroad or domestically. Growth in average household income in India is expected to be 6 to 7 percent annually from 2008 to 2023, further broadening the Indian middle class and increasing disposable income, and thus further increasing the potential market for new drugs.[62]

Sales of pharmaceuticals in India have expanded more rapidly than in other markets in recent years. Drug sales increased 9 percent over the period of 1996 through 2006, as compared to a 7 percent growth rate globally.[63] Although total R&D spending at Indian pharmaceutical companies is still a relatively small 4 percent of total turnover,[64] there are nonetheless signs of a shift toward research. In 2007, "as many as twelve [Indian] companies engaged in research for new pharmaceutical substances."[65]

III. CURRENT STATE OF INDIAN PHARMACEUTICAL PATENT LAW

A. Overview

The controversial revised Section 3(d) has raised questions around the world about India's compliance with the spirit if not the letter of its obligations under TRIPS.

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[56] *Id.* § 25(1)(e).
[57] *Id.* § 25(2)(e).
[58] *Id.* § 25(3)(b).
[59] Uwe Perlitz, *India's Pharmaceutical Industry on Course of Globalisation*, DEUTSCHE BANK RESEARCH, 5 (Apr. 9, 2008), http://www.dbresearch.com/PROD/DBR_INTERNET_EN—PROD/PROD0000000000224095.pdf.
[60] Janice Mueller, *The Tiger Awakens: The Tumultuous Transformation of India's Patent System and the Rise of Indian Pharmaceutical Innovation*, 68 U. PITT. L. REV. 491, 542 (2007).
[61] *Id.*
[62] Perlitz, *supra* note 61, at 6.
[63] *Id.* at 4.
[64] *Id.* at 7.
[65] *Id.* If the trend continues, Indian companies could conceivably be expected to be more embracing of TRIPS and the protections for innovation that the TRIPS framework provides for member States. The presence of a highly skilled workforce and relatively low development costs also increase the attractiveness of India as a site for future pharmaceutical R&D.

The *Novartis* case (discussed in detail below) is the first direct legal challenge to Section 3(d) in Indian courts.[66]

As discussed previously, the revised section provides no real guidance, either in the body of the section or in the explanatory comments, on what threshold of "enhanced efficacy" must be met in order to patent a new form of a known chemical entity. Given the importance of evergreening to product portfolio management strategies and to return on investment for pharmaceutical innovator companies,[67] it is not at all surprising that the unusual provisions of Section 3(d) would eventually be challenged by an international company in Indian courts.

B. Novartis' Challenge to Section 3(d)

1. Factual and Procedural Background

Novartis researchers, building on previous research into possible treatments for a form of cancer called chronic myelogenous leukemia, discovered in the early 1990s a promising drug called imatinib.[68] Novartis filed a patent application in the United States in 1993 covering both imatinib as a free base and its pharmaceutically acceptable salts.[69] As a result of further research, Novartis identified the beta crystalline form of the mesylate salt of imatinib as an improved and more pharmaceutically stable form of the molecule.[70] Imatinib mesylate was approved by the Food and Drug Administration in 2001 and launched in the United States as Gleevec.

As discussed above, drug product patents were unavailable in India until January 1, 2005. However, as per the interim procedures established by the Patent (Amendment) Act of 1999,[71] Novartis filed an Indian application claiming the mesylate salt of imatinib under the mailbox provisions discussed previously.[72] As was its right under the 1999 Act,[73] Novartis also applied for and was granted exclusive marketing rights (EMR) during the pendency of its patent application for imatinib mesylate, known by the brand-name Glivec in India.[74]

Based on the rights granted to it by the EMR, Novartis filed suit before the High Courts of Madras and Bombay against generic manufacturers who had been manufacturing imatinib mesylate and selling it under various trade names at a lower price

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[66] Sheehe, *supra* note 28, at 583.

[67] *Id.* at 584.

[68] Shamnad Basheer & T. Prashant Reddy, *The "Efficacy" of Indian Patent Law: Ironing out the Creases in Section 3(d)*, 5 SCRIPTED 232, 235 (2008), *available at* http://www.law.ed.ac.uk/ahrc/script—ed/vol5—2/basheer.asp.

[69] Pyrimidine derivatives and processes for the preparation thereof, U.S. Patent No. 5,521,184 (filed Apr. 28, 1994).

[70] Basheer & Reddy, *supra* note 70, at 235.

[71] 1999 Amendment, *supra* note 48.

[72] Crystal modification of a N-phenyl-2-pyrimidineamine derivative, processes for its manufacture and use, India Patent App. No. 1602/MAS/98 (filed July 17, 1998).

[73] 1999 Amendment, *supra* note 48.

[74] Feroz Ali & Rishi Kumar M. Dugar, *Patently Confusing: Same Problem, Differing Verdicts*, PHARMA PATENTS (Dec. 11, 2005, 5:01 PM), http://pharmapatents.blogspot.com/2005_12_01_archive.html.

than Novartis' Glivec.[75] The Madras High Court upheld the EMR and issued a restraining order against the generic manufacturers as requested.[76] In reaching its decision, the Madras High Court acknowledged that Novartis had overcome any public interest barrier to the granting of an injunction with the patient assistance program it had in place (Glivec International Patient Assistance Program or "GIPAP").[77]

The Bombay High Court[78], on the other hand, disagreed with the Madras Court's assessment on the request for injunction, citing the defendants' substantial challenges to the validity of Novartis' EMR, and "the fact that the [Novartis] drug was more expensive and was being imported . . . (triggering fears of [risk to] sustained supplies of such a critical life-saving drug in India)."[79]

Novartis' patent application faced pre-grant opposition by several generic manufacturers and one non-governmental organization, the Cancer Patients Aid Association, on the following grounds: a) lack of novelty/anticipation; b) lack of significantly enhanced efficacy under Section 3(d); c) obviousness, and; d) wrongful priority.[80] The Assistant Controller of Patents ultimately rejected Novartis' patent application on the grounds noted above.[81]

Pursuant to the rejection of its patent application, Novartis filed two writ petitions in the Madras High Court: an appeal to the Assistant Controller's rejection order and a challenge to the validity of Section 3(d) on the grounds of unconstitutionality and incompatibility with India's obligation under TRIPS.[82] The first claim was transferred to a specialized appellate tribunal known as the Intellectual Property Appellate Board (IPAB) for review.[83] The claims in the second petition are at the heart of this work and will be discussed at length below.

2. A "Head-On" Challenge to Section 3(d)

As discussed above, the revised Section 3(d) excludes from patentability a compound representing "the mere discovery of a new form of a known substance."[84] In rejecting Novartis' patent application, the Indian Patent Office "held [inter alia] that the patent application offered a new form of a known substance and did not demonstrate any improvement in efficacy."[85] Novartis strongly disputed this notion, contending that imatinib mesylate did not fall under the exclusions to patentability found in Section 3(d).

An expert opinion was submitted to the Indian Patent Office which demonstrated that a thirty percent increase in bioavailability was noted in the β-

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[75] Feroz Ali & Rishi Kumar M. Dugar, *Patently Confusing: Same Problem, Differing Verdicts*, PHARMA PATENTS (Dec. 11, 2005, 5:01 PM), http://pharmapatents.blogspot.com/2005_12_01_archive.html.

[76] Novartis AG v. Adarsh Pharma., 2004 (29) P.T.C. 108 (Mad.)

[77] Basheer & Reddy, *supra* note 70, at 237.

[78] Novartis AG v. Mehar Pharma., 2005 (30) P.T.C. 160 (Bom.).

[79] *Id.*

[80] *Id.*

[81] Indian Patent Office, Patent App. No. 1602/MAS/98 [hereinafter IPO Decision] (filed July 17, 1998) (rejected Jan. 25, 2006).

[82] Basheer & Reddy, *supra* note 70, at 237.

[83] *Id.*

[84] 2005 Amendment, *supra* note 50, § 3(d).

[85] Sheehe, *supra* note 28, at 587.

crystalline form of the mesylate salt of imatinib relative to its free base form.[86] However, the Assistant Controller did not accept Novartis' assertion that the relative increase in bioavailability constituted a "significant improvement in efficacy."[87] Further, the Controller rejected, without in-depth comment, Novartis' contention that imatinib mesylate is a new product because the crystal form is not an inherent property of imatinib acid addition salt exhibiting polymorphism and human intervention was necessary in order to produce the subject compound.[88] In light of its failure to persuade the IPO of the inapplicability of Section 3(d) to the Glivec patent, Novartis pursued relief through both a patent appeal through the IPAB and (of most interest here) a judicial appeal in the form of a declaration that Section 3(d) is unconstitutional and/or incompatible with India's obligations under TRIPS as a WTO member. Both of Novartis' arguments for invalidation of Section 3(d), as well as the High Court's analysis, are discussed in more detail below.

3. Claim of Unconstitutionality under Article 14 of the Indian Constitution

Novartis argued in its writ petition that the lack of express guidelines in determining sufficient enhancement of efficacy for derivative compounds provided the Patent Controller with uncontrolled discretion to apply his or her own standard in an arbitrary and potentially unequal fashion.[89] Novartis contended that without clear legal standards accompanying the revised section, patent protection could be denied arbitrarily based on the examiner's whim in violation of the Equal Protection provisions[90] of the Indian Constitution, even in cases where improved clinical efficacy of a derivative compound has been demonstrated.[91]

The Indian government argued that what constitutes a sufficient improvement in efficacy could be scientifically established by the experts in the field, implying that there is already a common understanding of the meaning of the terms in the industry and in the Indian Patent Office.[92] Further, it argued that even if the Patent Controller wrongly rejects an application, "such a decision could always be corrected by the Appellate Authority and then by higher forums."[93] The Court, in discussing the meaning of the term "efficacy" chose to confine itself to analyzing the definition found in Dorland's Medical Dictionary rather than consulting a more general English dictionary.[94] This seems to suggest an assumption on the part of the Court that efficacy must be construed as "therapeutic efficacy", thus making the statutory section applicable only to pharmacologically active substances and not to other chemical classes such as agro-chemicals.[95]

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[86] IPO Decision, *supra* note 83, at 4.
[87] *Id.*
[88] *Id.* at 2.
[89] *Novartis AG v. Union of India*, 2007 A.I.R. 24759 (Madras H.C.) at ¶ 3.
[90] INDIA CONST. art. 14 ("The State shall not deny to any person equality before the law or the equal protection of the laws within the territory of India.").
[91] *Novartis*, 2007 A.I.R. 24759 at ¶ 3.
[92] *Id.* at ¶ 4.
[93] *Id.*
[94] *Id.* at ¶ 13.
[95] Basheer & Reddy, *supra* note 70, at 244.

The High Court concluded that any apparent ambiguity in the definition of what constitutes a significant difference in efficacy—or even in the definition of the term "efficacy" itself[96]—was intended by the Parliament in order to avoid fixing a specific formula to be applied in all situations without regard to the particular facts of a case.[97] Once the Court reached an understanding of the legislative intent behind Section 3(d), rules of statutory construction compelled it "to give the statute a purposeful or functional interpretation."[98] Accordingly, the Court made significant findings on the widespread concern by members of Parliament that without limitations imposed by Section 3(d) as amended,[99] patenting of pharmaceuticals would foreclose access to life-saving medicines for the common man and would lead to widespread evergreening.[100]

The Court found that the legislative body, who were not technical experts, intended to provide the Patent Controller with a high degree of discretion to deal with both present and future technologies on a case-by-case basis.[101] The High Court "highlighted that merely because legislation is skeletal and does not contain definitions or guidelines, it does not necessarily mean that [the statute] is arbitrary."[102] The Court appears to have concluded that this legislative delegation of the technical decision-making to the Indian Patent Office for Section 3(d) was appropriate, as the function was considered to be a "non-essential legislative function."[103]

Regarding the fundamental constitutional question, the Court found a "broad distinction between discretion which has to be exercised with regard to a fundamental right guaranteed by the Constitution and some other right which is given by [a] statute."[104] The Court concluded that the statutory patent rights in question fall into the latter category.

In order to mount a successful challenge to a statute conferring such discretionary powers, a litigant must show that there is both a "possibility of a real and substantial discrimination and [that] such exercise [of discretion] interferes with [a] fundamental right guaranteed by the Constitution."[105] Further, the Court may not presume that the authorities will administer a law with wide discretionary latitude in an abusive manner in order to invalidate a law.[106] The only two grounds available for invalidating a law passed by Parliament are violation of a fundamental constitutional right and legislative incompetence,[107] neither of which Novartis established to the satisfaction of the High Court.

As such, the Court held that Section 3(d) is not in violation of Article 14 of the Constitution of India.[108] The Court determined that legislative intent in adopting the amended Section 3(d)—to prevent evergreening and to provide easy access by citizens to

[96] *Novartis*, 2007 A.I.R. 24759 at ¶ 14.
[97] *Id.* at ¶ 11.
[98] *Id.* at ¶ 12.
[99] 2005 Amendment, *supra* note 50, § 3(d).
[100] *Novartis*, 2007 A.I.R. 24759 at ¶ 12.
[101] *Id.* at ¶ 14.
[102] Basheer & Reddy, *supra* note 70, at 241.
[103] *Id.* at 242.
[104] *Novartis*, 2007 A.I.R. 24759, at ¶ 16.
[105] *Id.*
[106] *Id.* at ¶ 17.
[107] *Id.* at ¶ 18.
[108] *Id.* at ¶ 19.

life-saving drugs—was appropriate and constitutionally sound.[109] Further, the appellate channels available to unsuccessful patent applicants were deemed sufficient to prevent abuses of discretion.[110]

4. Challenge to the Compatibility of Section 3(d) with TRIPS Obligations

The primary thrust of Novartis' argument around the incompatibility of Section 3(d) with TRIPS centers around Article 27 of the TRIPS agreement. Article 27 requires that patent protection is made available "for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application."[111] Novartis asserted in its petition that by including the enhanced efficacy requirement in the amended section, India was in fact depriving inventors of the guaranteed right to have an invention patented as required by Article 27 of TRIPS.[112]

The Indian government argued in response to Novartis' petition that TRIPS member states possessed wide latitude in crafting local laws to meet the member's obligations under TRIPS.[113] The government further asserted that as "a welfare country . . . [India's] first obligation under the Constitution is to provide good health care to its citizens."[114] India maintained that in meeting its constitutional commitment to health care for its citizens, it "has every right to bring in any local law in discharging . . . obligations under TRIPS to suit to the needs and welfare of its citizens."[115]

Counsel for the government also cited case law supporting the notion that Indian courts do not have jurisdiction to test the validity of local laws on the grounds of incompatibility with international treaty obligations, particularly when the local law is intended to ensure the welfare of the local entities' citizens.[116] Novartis, citing English case law,[117] asserted in response that even if the Court lacked jurisdiction to strike down the disputed law, there was no express or implied bar to the Court providing a declaratory judgment declaring the disputed section of the law in violation of international treaty obligations.[118]

In finding for the government, the Court distinguished the facts of *Equal Opportunities Commission*[119] on the basis that the European Union directive in dispute in that case had been "domesticated as domestic law in England" subsequent to its adoption, giving the domestic courts jurisdiction over the provisions of the law.[120] In contrast, the Court agreed with counsel for the government that in the instant case, the TRIPS

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[109] *Id.*
[110] *Id.*
[111] TRIPS Agreements, *supra* note 7, art. 27.1.
[112] *Novartis*, 2007 A.I.R. 24759, ¶ 3.
[113] *Id.* at ¶ 4.
[114] *Id.*
[115] *Id.*
[116] *Id.*
[117] In particular, Novartis cited *Equal Opportunities Commission & Another v. Secretary of State for Employment*, (1995) 1 A.C. 6–7 (House of Lords declaration that a domestic law was incompatible with EU treaty obligations, in response to an appeal in a private citizen's employment discrimination suit).
[118] *Novartis*, 2007 A.I.R. 24759, ¶ 6.
[119] *Equal Opportunities Commission*, *supra* note 119.
[120] *Novartis*, 2007 A.I.R. 24759, ¶ 7.

agreement provisions could not become law in India absent further legislative action by Parliament,[121] and thus could not be enforced directly by Indian courts, forcing petitioner to seek a remedy in a "forum other than the domestic court."[122] In holding that "when a domestic law is challenged on the ground of it being in violation of an International Treaty, domestic courts would have no jurisdiction,"[123] the Court cited controlling English precedent as the basis for this rule.[124]

The TRIPS compatibility question at issue in the case was framed by the *Novartis* Court as a contracts question, with the parties to the contract being the government entities who are signatories to the Agreement.[125] As such, the Court determined that in disputes about compliance with international treaties, it must analyze the terms of the treaty itself, including any provision for settling disputes contained within the body of the treaty.[126] Since a centralized dispute resolution procedure exists under TRIPS[127] and accompanying WTO Rules and Procedures, the High Court concluded that domestic courts were not the appropriate forum for resolving disputes over compliance with the agreement.

5. The Story Continues

IPAB rejected Novartis' appeal of the denial of its Glivec patent application in June 2009. The Board determined that while the beta crystalline form of imatinib was both novel and inventive, it cannot be patented under Section 3(d) because Novartis had failed to demonstrate significantly enhanced efficacy of the new form. The final IPAB decision recited two statutory grounds for rejecting the patent. In addition to affirming the rejection on 3(d) grounds, the Board also very controversially and inexplicably invoked the public order provisions of section 3(b), holding that Novartis' monopoly price of 120,000 rupees per patient per month would be against the interests of public order.[128]

This holding will almost certainly be challenged further by Novartis at the Indian Supreme Court, and may additionally be appealed by the Swiss government directly to the WTO dispute resolution body. Post-grant invocation of compulsory licensing provisions is available under TRIPS to address true public health situations and alleged price gouging,[129] thus allowing for post-grant regulation of the use or abuse of a patent.[130] The IPAB decision in this respect appears to be completely at odds with the patentability requirements as spelled out in the TRIPS agreement,[131] and will most likely be subject to further credible challenge by Novartis.

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[121] *Id.*
[122] *Id.*
[123] *Id.*
[124] *Ellerman Lines, Ltd. v. Murray*, [1931] A.C. 126.
[125] *Novartis*, 2007 A.I.R. 24759, ¶ 8.
[126] *Id.*
[127] TRIPS Agreements, *supra* note 7, art. 64.1.
[128] *Novartis Moves SC in Glivec Patent Case*, THE ECONOMIC TIMES (Aug. 29, 2009), http://economictimes.indiatimes.com/News/News-By-Industry/Healthcare-/-Biotech/Novartis-moves-SC-in-Glivec-patent-case/articleshow/4947085.cms.
[129] TRIPS Agreements, *supra* note 7, art. 31.
[130] *Novartis Moves SC in Glivec Patent Case*, *supra* note 130.
[131] TRIPS Agreements, *supra* note 7, art. 27.1.

C. Roche v. Cipla

1. Background

The issue of patent protection for incremental improvements to drugs and what constitutes "enhanced efficacy" for purposes of section 3(d) was once again the central theme in *Roche v. Cipla*. Specifically, the patent at issue attempted to protect a new form of a known compound, which Roche unsuccessfully argued met the 3(d) threshold for increased efficacy by an improvement in its thermodynamic stability and thus the pharmaceutical properties of the molecule.

The dispute between F. Hoffman-La Roche Ltd. and Cipla Ltd. revolved around the drug erlotinib, a cancer therapy intended to treat advanced or metastatic non-small cell lung cancer. A second plaintiff, OSI Pharmaceuticals, Inc., jointly held an Indian patent with Pfizer Products, Inc. covering erlotinib hydrochloride, a patent granted on February 23, 2007 as Indian Patent No. 196774.[132] Roche was granted a license to use, sell, and offer for sale erlotinib and other products, and to enforce any infringement of property rights associated with the licensed products pursuant to a 2001 development collaboration and licensing agreement between OSI and Roche.[133] Roche began importing and selling the drug in India in 2006 under the brand name Tarceva.

In January 2008, Cipla launched a print and electronic media campaign to announce its intention to launch a generic version of Roche's Tarceva.[134] Cipla's version of the drug was to be sold as Erlocip.[135] Roche filed suit on January 15, 2008, seeking an interim injunction to prevent Cipla from infringing on plaintiff's patent with respect to Tarceva.[136] Cipla cross-claimed seeking invalidation of Roche's erlotinib patent on various grounds, including incompatibility of the patent application with Section 3(d) of the Patent Act. There were also allegations that Roche had failed to make Tarceva readily available or affordable in spite of being granted regulatory approval to import and sell the product in India in 2005.[137] In addition to the claim that insufficient supplies were made available to the Indian market of the foreign-manufactured Tarceva, Cipla noted that each tablet of Tarceva was being priced at 4,800 rupees, while Cipla's Erlocip was priced at 1,600 rupees. Roche's petition for an injunction was initially denied in March 2008, at which time Roche unsuccessfully sought an appeal from a two-judge panel of the Division Bench of the High Court of Delhi.[138]

2. Obviousness and Section 3(d)

In seeking to invalidate Roche's patent and thus avoid an injunction preventing the sale of Erlocip, Cipla raised a number of issues regarding the '774 patent. These issues included lack of full disclosure of crystal form information in the '774 application,

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[132] Indian Patent No. 196774 (issued Feb. 23, 2007). An official notice of the patent's issuance can be found at the Controller General of Patents Designs and Trademarks website, http://ipindia.nic.in/ipr/patent/journal_archieve/journal_2007/patent_journal_2007.htm (click on the link corresponding to July 13, 2007, Part II, at page 26313).

[133] F. Hoffman-La Roche, Ltd. v. Cipla, Ltd., Delhi H.C., FAO (OS) 188/2008, ¶ 5.

[134] *Id.* at ¶ 6.

[135] Basheer & Reddy, *supra* note 70, at 252.

[136] *Id.* at ¶ 8.

[137] *Id.* at ¶¶ 52, 81.

[138] *Id.* at ¶ 1.

Roche's failure to completely disclose the specification of the product whose patent was allegedly infringed, and failure by Roche to demonstrate the requisite enhanced efficacy under Section 3(d) in order to be granted a patent on a substance derived from a previously known compound.

The Section 3(d) issue arose because erlotinib hydrochloride was considered to be a derivative of a compound known as quinazoline, which had been previously disclosed by at least three European patents dating back to 1993.[139] One of those patents disclosed the exact chemical structure of Roche's patent with the exception of a single substitution which was considered "obvious to any person skilled in the art."[140]

Roche attempted to claim that erlotinib hydrochloride (specifically its polymorph B form) was not excluded from patentability due to Section 3(d) issues. Roche asserted that form B is "thermodynamically more stable . . . [providing] improved oral dosage in solid form,"[141] thereby attempting to meet the 3(d) threshold for substantially increased efficacy by establishing a significant improvement in stability and bioavailability. In addition to its unfavorable findings on the nondisclosure issues mentioned above, the High Court found that the increased formulation stability of the polymorph B form found in Tarceva did not meet the Section 3(d) threshold for a substantial improvement in efficacy required to sustain Roche's patent.[142]

D. Future implications for Innovator Companies in India

The application of Section 3(d) as it was interpreted in *Novartis* is sure to have lasting implications for pharmaceutical innovator companies hoping to protect their intellectual property in India. Indeed, since the *Novartis* decision, the office of the Patent Controller in India has denied other patent applications by multi-national companies on Section 3(d) grounds. German company Boehringer Ingelheim filed an application in India for a new pediatric form of its HIV drug nevirapine.[143] Two patient advocacy groups filed pre-grant opposition to Boehringer's patent application, relying heavily on the *Novartis* case and the Court's interpretation of the word efficacy.[144] Boehringer asserted that the new form of nevirapine at issue exhibited a more stable particle size distribution which led to increased stability for the aqueous solution formulation developed for pediatric use.[145] Boehringer's patent application was denied on the grounds that no evidence was presented of a novel formulation providing significantly enhanced therapeutic effect as compared to other known forms of the drug.[146]

Section 3(d) as applied to date appears to exclude from patentability new salt forms as well as new polymorphic forms of previously known substances. Exclusion of

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[139] *Id.* at ¶ 13.
[140] *Id.*
[141] *Id.* at ¶ 33.
[142] *Id.* at ¶ 60.
[143] Indian Patent Application number 2485/DEL/1998, "Pharmaceutical Composition."
[144] Boehringer Ingelheim Pharmaceuticals (Application No. 2485/DEL/1998) v Indian Network for People Living with HIV/AIDS (INP+) and Positive Womens Network (PWN), Delhi Patent Office (2008), http://www.i-mak.org/pharma-patent-decisions/.

[145] *Id.* at 10.
[146] *Id.* at 14.

such new forms seems to be without regard to any improvement in properties such as bioavailability or physical or chemical stability of the drug. Further, in interpreting 3(d) to require a "substantial" increase in therapeutic efficacy of such a drug as a condition of patentability, the Indian courts have provided neither quantitative nor qualitative guidance on what constitutes a sufficient increase in efficacy.

As discussed further below, this uncertainty could have a substantial impact on the life-cycle management strategies of pharmaceutical innovators, particularly since those strategies have historically relied heavily on being first to market and then following on with incremental improvements in drug forms. India's current protectionist policies toward its domestic generic manufacturers could cause long-term harms to the industry and to India's citizens, either in the form of halting innovative R&D into new medicines, or discouraging some innovator companies from seeking to make their drugs available in India at all.

IV. A COMPARATIVE LOOK AT PHARMACEUTICAL PATENT PROTECTION IN THE UNITED STATES

While historically patent protection for pharmaceuticals has been much more readily available in the United States, recent case law developments could have important implications for pharmaceutical innovator companies seeking to maximize protection for their intellectual property portfolios. The following section outlines a brief history of pharmaceutical patent protection in the United States, as well as important recent developments in obviousness jurisprudence that could significantly impact innovators wishing to patent incremental improvements to pharmaceuticals.

A. Introduction and historical overview

The legal authority for patent protection of pharmaceutical (and other) innovations has its roots in the U.S. Constitution: "The Congress shall have Power . . . To 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."[147] Early pharmaceutical manufacturers in the United States generally chose not to seek patent protection for their product lines.[148] One company built on the success of others, and each company tended to have a full line of pharmaceutical products, competing instead on public perceptions of the quality associated with a manufacturer's name.[149]

By the end of the 19th century, pharmaceutical chemistry was dominated by German manufacturers who typically sought U.S. patents and subsequently licensed them to U.S. distributors.[150] This system became unworkable during the two World Wars, and Congress responded by passing the Trading with the Enemy Act to allow U.S. companies

[147] U.S. CONST. art. I, § 8.
[148] Dennis B. Worthen, *American Pharmaceutical Patents from a Historical Perspective*, INT'L J. PHARM. COMPOUNDING 36 (Nov.–Dec. 2003).
[149] *Id.*
[150] *Id.*

to break German patents for critical medicines.[151] The World Wars led the U.S. pharmaceutical industry into a new era of self-sufficiency through active research and discovery of new medicines, coupled with patenting of such discoveries, the basic model in place today.[152]

The Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act in 1962[153] significantly increased the regulatory burden on drug companies for approval of new drugs, requiring that companies prove efficacy and safety prior to approval, in contrast to the previous requirement that companies merely demonstrate safety.[154] The net effect of this change as it was applied by the Food and Drug Administration was an increasing "drug lag," or steadily increasing length of time for review and approval of new drug applications (NDAs),[155] and a *de facto* decrease in the available patent term for new drugs.[156]

The Waxman-Hatch Drug Price Competition and Patent Restoration Act of 1984[157] provided, among other things, for up to a five-year extension of patent exclusivity from date of issuance for NDA holders in order to compensate for the increased exclusive marketing time lost to regulatory review of the NDA.[158] It also contained provisions for a 3-year extension for companies undertaking additional clinical work to support a change in dosage or salt form, or in support of adding a new clinical indication to the product label, as well as a 6-month extension when studies were conducted to support pediatric use of a product.[159]

It is also worth noting that one legislative goal of Waxman-Hatch was to foster the introduction of generic drugs into the marketplace.[160] Concessions to the generic industry were included to counterbalance the exclusivity relief granted to innovator companies. The concessions included the creation of the Abbreviated New Drug Application (ANDA) process, wherein generic manufacturers are no longer required to repeat the safety and efficacy testing necessary to register a new drug, but merely need to prove bioequivalence to the approved innovator product. The FDA standard for bioequivalence for generic "follow-on" drugs is demonstrated absorption that is in the range of 80-125% of that observed by the name brand product.[161] Thus, a generic drug that is only 81% orally bioavailable relative to the innovator drug is sufficiently equivalent to be granted marketing approval. The Act also makes allowances for generic manufacturers to begin testing their product for the limited purpose of establishing the require bioequivalence prior to the lapse of the innovator's patent. In practice, the first

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[151] Trading with the Enemy Act of 1917, ch. 106, 40 Stat. 411.
[152] Worthen, *supra* note 150, at 37.
[153] 1962 Food, Drug and Cosmetic Act Amendments, Pub. L. No. 87-781, 76 Stat. 780.
[154] Worthen, supra note 150, at 39.
[155] *Id.*
[156] *Id.*
[157] Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.
[158] *Id.*
[159] *Id.*
[160] *Id.*
[161] *See* UNITED STATES FOOD AND DRUG ADMINISTRATION, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS § 1.3 (30th ed. 2010*), available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

generic manufacturer out of the starting gate can normally be ready to launch as soon as the innovator's patent expires.[162]

The Act further provided for an 180-day marketing exclusivity period for the first generic company to file a successful ANDA.[163] Despite the general hype about drug pricing and the enthusiasm for generic drugs among the public and insurers, during the 180-day exclusivity period for the first approved generic, prices for the generic normally remain very close to the brand name prices.[164] It is only after other generic competitors are allowed to enter the market that any real shift in price from the name brand pricing is observed. In this regard, the first to market generic company is absorbing as much profit as possible during the exclusive period, just as the innovator does to recover its initial investment. It could reasonably be argued that such an exclusive recovery period is required in order to incentivize *anyone* to bring a drug to market, a point that gets lost in the argument when profit making by large multinational pharmaceutical is discussed with disdain.

B. Non-Obviousness and Pharmaceutical Patents

1. General Requirements for Patentability in the United States

The basic requirements for patentable subject matter (regardless of the field of endeavor) are novelty,[165] utility[166] and non-obviousness.[167] Also required under 35 U.S.C. § 112 is that the inventor "meet certain drafting and disclosure criteria so as to return value to society in the form of technical information via the patent disclosure."[168] Such disclosure ensures that public knowledge in the art in question is increased as compensation to society for the temporary exclusivity granted to a patent holder.[169]

New active pharmaceutical ingredients (API) are typically covered by composition of matter patent claims, whereas process claims typically cover methods of making or using the active ingredient.[170] More problematic from a patentability and patent defense standpoint are the later incremental improvements that have been the central focus of this work, such as new salt or polymorphic forms of known chemical entities. Case law relevant to this problem area is discussed below.

2. 35 U.S.C. § 103 and Non-Obviousness Jurisprudence Before *KSR*

Section 103 excludes from patentability on obviousness grounds any invention representing an incremental improvement on the prior art

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[162] Worthen, *supra* note 150, at 40.

[163] Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

[164] *See* Jarrett Murphy, *Generic Drug Prices Rising Rapidly*, CBS NEWS (Dec. 27, 2002), http://www.cbsnews.com/stories/2002/12/27/health/main534528.shtml.

[165] 35 U.S.C. § 102 (2006).

[166] 35 U.S.C. § 101 (2006).

[167] 35 U.S.C. § 103 (2006).

[168] Michael Enzo Furrow, *Pharmaceutical Patent Life—Cycle Management after* KSR v. Teleflex, 63 FOOD & DRUG L.J. 275, 288 (2008) (citing 35 U.S.C. § 112).

[169] Worthen, *supra* note 150, at 37.

[170] *Id.* at 289.

> if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.[171]

While "[c]ourts have developed well-settled standards for utility, novelty and proper specification drafting[,] . . . [n]on-obviousness . . . has been comparatively less amenable to tight judicial standards."[172] The *KSR* decision, which will be discussed in detail below, appears to be a response by the U.S. Supreme Court to such previous uncertainty around obviousness jurisprudence.[173]

However, prior to the *KSR* decision, there was certainly at least rough guidance in the case law regarding the level of inventiveness required to render an invention non-obvious. For example, the Supreme Court in *Great Atlantic & Pacific Tea Co.*, in overturning the lower courts' refusal to invalidate the plaintiff's patent on a new checkout device, explained that "[a]n invention need not be as startling as an atomic bomb to be patentable. But [it] has to be of such quality and distinction that masters of the scientific field in which it falls will recognize it as an advance."[174] The Court acknowledged that a significant possibility for actually stifling innovation and knowledge sharing could exist were patent protection granted to relatively minor advances "which would naturally and spontaneously occur to any skilled mechanic or operator in the ordinary progress of manufactures."[175]

The language in this relatively old case has likely become more important in the modern world of pharmaceutical development. As the tools and techniques of the industry continue to improve, technical and financial barriers to synthesizing and screening compound variants earlier in development continue to go down. These improvements potentially reduce the "inventive power" required to introduce a new salt, polymorphic or enantiomeric form of a known substance, and thus perhaps reduce the courts' willingness to routinely provide patent protection for such incremental improvements absent a showing of some compelling unexpected result with the new form.

Indeed, while the United States has historically been quite permissive with respect to patenting new forms of pharmaceutical substances representing incremental improvements in the art, a gradual shift away from that position seems to have been occurring as the technology and available research tools have improved dramatically. As discussed in the next section, *KSR* may represent a substantial shift away from *any* presumption of patentability of new forms of known pharmaceuticals absent completely unexpected results.

In the landmark case *Graham v. John Deere* in 1966, the Supreme Court outlined a three-part factual determination intended to assist the trial courts in the legal

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[171] 35 U.S.C. § 103(a).

[172] Furrow, *supra* note 170, at 276–77.

[173] *See id.* at 277.

[174] Great Atl. & Pac. Tea Co. v. Supermkt. Equip. Corp., 340 U.S. 147, 155 (1950) (A new product uniting old known elements in a new combination with no change in their respective functions was found to be un-inventive as it would be obvious to one skilled in the related mechanical arts.).

[175] *Id.* (quoting Atl. Works v. Brady, 107 U.S. 192, 200 (1883)).

analysis of the non-obviousness issue.[176] The factors to be considered by the trial courts under the *Graham* test are: 1) the scope and content of the prior art; 2) differences between the prior art and the claims at issue; and 3) the level of ordinary skill in the pertinent art. Secondary considerations such as "commercial success, long felt but unsolved needs, [or the] failure of others,"[177] can also be used by the patentee to establish the particular circumstances militating against a finding of obviousness or to rebut a finding of obviousness based on the 3-part test out lined above.
Likewise, in *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, the Supreme Court held that "while the combination of old elements performed a useful function, it added nothing to the nature and quality of the [relevant art] already patented."[178] The *Anderson's-Black Rock* Court also concluded that while combination of the old elements into the new apparatus did indeed solve the problem it sought to solve and was commercially successful, "more than that is needed for invention."[179]

The *Graham* test certainly appears to have left some room for a case-by-case evaluation of the value of an incremental invention relative to the level of ordinary skill in the art at any given time. However, one might also expect the Graham test and its associated "secondary considerations" to become more problematic for pharmaceutical innovators as the skill level and technological sophistication of the industry continue to improve. For example, in the case of enantiomers or stereoisomers of a pharmaceutical compound, it is well established in the industry that single enantiomer drugs are often preferable to racemic mixtures (50/50 mixtures of the optical isomers of a compound), both from a safety and an efficacy point of view.[180] The first *Graham* factor, the scope and content of the prior art, should lead a patent examiner (as well as the courts) to examine not only references that disclose the chemical structure of the compound, but also those that describe practical processes for resolving or separating enantiomers of the compound from each other, as well as the those pertinent to determining the pharmacological value of dosing a single isomer over a mixture.[181] Or as put another way by the *KSR* court (case is discussed in more detail below):

> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions.[182]

In addition to the factors outlined in the *Graham* Test, the Federal Circuit has also developed and previously applied another standard, a "teaching, suggestion, or motivation (TSM) test, under which a patent claim is only proved obvious if the prior art,

[176] Graham v. John Deere Co., 383 U.S. 1, 17 (1966).
[177] *Id.* at 17–18.
[178] Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62 (1969).
[179] *Id.* at 63.
[180] Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, ¶ 21.
[181] *Id.*
[182] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 401 (2007) (upholding the *Graham* factors, and rejecting a strict, formalistic application of the Federal Circuit's "teaching, suggestion or motivation" test).

the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings."[183]

> Subsumed within the Graham factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.[184]

The TSM test as developed by the Federal Circuit softened the non-obviousness bar established by the *Graham* factors in that the test requires an overt showing of some teaching, suggestion or motivation in the prior art or the knowledge base of those skilled in the pertinent art, which would "motivate… [an inventor] to combine prior art references to make the claimed invention."[185] However, all of this was revisited and arguably turned on its ear by the Supreme Court with the common sense evaluation developed in *KSR*.

3. KSR v. Teleflex and its potential impact on the future of pharmaceutical patent strategy

KSR v. Teleflex was a dispute over the validity of a patent held by Teleflex covering a particular design for an adjustable automobile accelerator pedal.[186] The district court held that the disputed claim in the Teleflex patent was obvious based on an analysis using the *Graham* factors.[187] The Federal Circuit reversed, ruling that "the district court erred as a matter of law by applying an incomplete teaching-suggestion-motivation test to its obviousness determination."[188] KSR appealed and the Supreme Court granted certiorari to review, ultimately overturning the decision by the Federal Circuit.[189]

The *KSR* decision creates an approach more flexible in its application of the TSM test for determining whether a person of ordinary skill in the art would have a reason to combine old elements in a new way.[190] The Supreme Court appears to have created "a very flexible 'reason to combine' test . . . [relieving] judges and examiners . . . [of] the need . . . to find explicit teachings in the prior art."[191] In its analysis, the Court also appears to have dispensed with the notion that courts and examiners need only look to the problem that the patentee is trying to solve or "that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to

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[183] *Id.* at 399.

[184] Pfizer, Inc. v. Apotex, Inc., 480 F. 3d 1348, 1361 (Fed. Cir. 2007) (Pfizer patent for a salt form invalidated on obviousness grounds).

[185] *Alza Co. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1295 (Fed. Cir. 2006).

[186] *KSR*, 550 U.S. 398 at 399.

[187] *KSR*, 550 U.S. 398 at 399–400.

[188] Teleflex, Inc. v. KSR Int'l Co., 119 Fed.Appx. 282, 290 (Fed. Cir. 2005).

[189] *KSR*, 550 U.S. 398 at 400.

[190] Furrow, *supra* note 170, at 305.

[191] *Id.* at 306.

solve the same problem."[192] In other words, the *KSR* Court would have reviewing courts and examiners cast a much broader net in their attempts to invalidate patents for obviousness based on the content of the relevant prior art. The emphasis on flexibility and common sense in the *KSR* opinion suggests a policy shift "intended to reduce the number of undeserving patents that slip through the non-obviousness net."[193]

Pfizer v. Apotex,[194] a case decided just prior to release of the *KSR* opinion, may have signaled the shift toward a more "flexible" obviousness determination that was coming with the *KSR* decision. *Pfizer* should in its own right raise some significant concerns regarding the future patentability of new forms of known drugs. In discussing the steps Pfizer had taken to select and optimize a salt form of its drug amlodipine, the Federal Circuit suggested a lack of an inventive step in the screening of pharmaceutical salts, since such screening is now routine in the drug development process in the industry:

> At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine. Creating a "product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal-and even common-sensical."[195]

In invalidating Pfizer's patent for the besylate salt of the drug amlodipine following a challenge by a generic manufacturer seeking an ANDA approval for the drug, the Federal Circuit determined that a skilled artisan would have been motivated to combine prior art references to achieve the claimed invention[196] and would also have had a reasonable expectation of success in doing so.[197] Further, it found that substituting the besylate salt for the earlier maleate salt form that had created issues of sticky tablets would have been obvious to try for one skilled in the art attempting to solve this particular problem.[198]

Inherency may also invalidate follow-on patents for new salt or polymorphic forms of existing drug molecules. An inherent disclosure need not be explicitly found in a prior art reference but instead is said to arise naturally from the teachings of the prior art. A lead case in this regard is *Schering Corp. v. Geneva Pharms, Inc.*, wherein the Federal Circuit invalidated Schering's patent for an active metabolite of its allergy drug loratadine, marketed as Claritin, on the grounds that the metabolite was inherent in the chemical space protected by the original loratadine patent.[199] The *Schering* court held that "a limitation or the entire invention is inherent and in the public domain if it is the

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[192] *KSR*, 550 U.S. 398 at 402.
[193] Furrow, *supra* note 170, at 307.
[194] Pfizer, Inc. v. Apotex, Inc., 480 F. 3d 1348, 1361 (Fed. Cir. 2007).
[195] *Pfizer*, 480 F.3d 1348 at 1371 (quoting *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006)).
[196] *Pfizer*, 480 F.3d at 1362.
[197] *Id.* at 1364.
[198] *Id.* at 1368.
[199] *Schering Corp. v. Geneva Pharms, Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003).

'natural result flowing from' the explicit disclosure of the prior art."[200] Fundamentally underlying this principle is the idea that limitations that are inherently found in the prior art are already in the public domain and therefore not patentable.[201]

While in the *Schering* case the invalidated patent covered subject matter that resulted naturally from the prior art through metabolism in a human body, it is conceivable that the concept of anticipation through inherency could be applied to new salt and polymorphic forms as well. From a prior art disclosure of the parent molecule it could fairly easily be argued that "a person of ordinary skill in the art could practice the . . . [the new form] without undue experimentation"[202] based on the teachings in the prior art. This is particularly true given advancements in the pharmaceutical arts and the routine practice in drug discovery of screening new drugs to find the best salt and polymorphic forms to take into further development. Such trends, if they continue, could move the United States farther away from the historically liberal grant of incremental improvement patents for pharmaceuticals and toward a less favorable climate for protection of subsequent improvements to existing drugs.

V. DISCUSSION AND CONCLUSION

Indian law is fairly clear in its hostility to patent protection for new forms of pharmaceuticals, having set a seemingly arbitrary but nearly total bar to any such protection for new salt or polymorphic forms of known drugs. The United States, historically much more liberal in the grant of such patents, is similarly moving toward a more stringent threshold for new pharmaceutical forms. In the long run, there is certainly some risk that well-intentioned policies in both countries which tend to favor generic entry into the marketplace could very well reduce available money and motivation for innovation, thereby stifling investment in new drug research and development. Such an outcome would be a case of "the cure being worse than the disease" since pharmaceutical advances would grind to a halt in such a scenario.

In the wake of the *KSR* decision, it seems clear that innovators, in order to be granted U.S. patent protection for new forms of known active ingredients, will need to show some substantial increase in efficacy or some other result that is completely unexpected when viewed relative to all of the relevant prior art. While less favorable in this regard to innovators than in the past, the U.S. climate still stands in fairly stark contrast to India, where it is not at all clear today that there is indeed *any* efficacy threshold that would satisfy the uniqueness requirements of Section 3(d).

India's current statutory patent regime, while arguably complying with the letter of TRIPS, appears to violate the spirit of the TRIPS agreement by imposing an arbitrary "therapeutic efficacy" threshold for patentability on incremental pharmaceutical inventions. This additional requirement is outside the scope of requirements for patentability as outlined in TRIPS (i.e. the invention must be new, involve an inventive step and must be capable of industrial application). Whether the Indian requirements under Section 3(d) will be challenged or could be successfully challenged at the WTO level remains to be seen. However, the provisions should certainly cause concern among

[200] *Id.* at 1379.
[201] *Id.* at 1379.
[202] *Id.* at 1381.

international pharmaceutical companies seeking to protect and market their products in India.

It is also interesting to note that while the patent climate in India is unfriendly to foreign pharmaceutical innovators, Indian companies are very aggressively pursuing pharmaceutical market share in the United States. The United States is India's largest export market for pharmaceuticals and in the years 2007 and 2008, Indian companies accounted for one out of every four ANDA approvals in the United States.[203] One could certainly hope that this apparent entrepreneurial spirit and increasing comfort in litigating associated patent cases in the United States will lead to recognition that patent protection is essential for a robust pharmaceutical R&D pipeline. Further, such protection, with the appropriate human welfare safeguards provided for in the TRIPS framework, is in our collective best interest in the long run.

As discussed previously, even in the world of generics development, some guarantee of return on investment is needed to ensure sufficient incentive to bring drugs to market. This proposition holds more strongly when the stakes are higher, as in the case of the extraordinary expenditures and risks an innovator company must incur in order to successfully bring one completely new drug to market. Without the incentives that patent protection and exclusivity provide, drug innovation may be stifled, contrary to humankind's continuing need for new and better drug therapies.

Given the overall climate of hostility to patent protection for drugs in India, an important emerging market, and the changing climate in the United States regarding patent protection for incremental drug improvements, innovator companies should probably reconsider their portfolio management strategies. The established model generally values return on investment for new development projects based on the idea of speed to market (i.e. being first) with an adequate form and formulation of the new drug. The initial work is normally then followed up with additional development to improve the molecule or its presentation—for example, reducing cost of goods through process improvements, improving shelf-life or drug delivery through new chemical or physical forms of the active ingredient, development of a more palatable or convenient dosage form, etc. Another undeniable component of this strategy is protecting underlying return on investment by achieving the maximum possible exclusivity for the innovator's drug. This latter part of the equation is certainly a very difficult sell, politically and from a public relations standpoint, but important nonetheless to companies investing (and risking) huge sums in R&D to initially bring new drugs to market.

In light of the current legal framework in the United States and India, the bar for patent protection for incremental improvements to existing drugs has been raised, and such protection cannot be taken for granted. If reaching an acceptable long-term return on investment ("ROI") for developing a new drug absolutely requires the ability to "evergreen" the franchise with later incremental improvements in drug form, it may be advisable for the innovator company to reconsider development of that particular drug in the first place. Even in cases where it makes sense to proceed with development anyway, albeit with a somewhat lower long-term ROI absent the ability to evergreen, accurately valuing the product to a portfolio will require taking into account the possibility that

[203] Deepak Kumar Jeena et al., *Presence of Indian Pharmaceutical Industries in US Market: An Empirical Analysis*, J. GENERIC MED. (Aug. 4, 2009), http://dx.doi.org/10.1057/jgm.2009.27.

patent protection may not be available for incremental improvements to existing drugs going forward.

It also behooves TRIPS member states in developing their laws within the TRIPS framework to seriously consider the value to the public good of some smaller, incremental improvements to existing drugs. Rather than paint all improvements with the same brush, it is worth considering the value of increased patient compliance (e.g. through better palatability or less frequent dosing) as well as the value of improved drug properties such as better drug stability over a drug's shelf life, increased bioavailability, and the like.