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REPORT

Drug Patenting in India: Potentially Lucrative, but a Difficult Task

By George Best and Photon Rao

Summary

In 2005, India responded to World Trade Organization pressure and changed its decades-old patent law to allow patents on pharmaceutical compounds. One of these changes, Section 3(d) of the Patents (Amendments) Act, 2005, has subsequently gained substantial notoriety among U.S. and European pharmaceutical companies. Section 3(d) mandates that ''salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, ''*unless they differ significantly in properties with regard to efficacy*.'' The Indian Patent Office has used this provision as the basis for refusing to grant, or invalidating upon pre- or post-grant opposition, patents covering a number of different drugs, including patents covering such potential blockbusters as Novartis's Glivec, Eli Lilly's Cialis, Bayer's Nexavar, and Gilead's Viread drugs.

There are, however, some signs that things might be changing for the better. Recently, the Madras High Court defined the term ''efficacy,'' as used in section 3(d). Moreover, the first ever drug patented in India, Roche's Pegasys (a pegylated interferon-α), survived a post-grant challenge brought by a prominent Indian manufacturer of protein drugs. A proper understanding of the efficacy standard and the scope of Section 3(d) terms such as *derivatives* will allow companies to enjoy exclusivity to sell their drugs in this very lucrative and growing market. Moreover, the provisions of Section 3(d) also are being evaluated, in India and internationally, for compliance on the WTO agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). This article looks at the structural as well as the efficacy aspect of Section 3(d), and the ongoing debate about Section 3(d)'s TRIPS compliance, to provide some clarity in this potentially lucrative, but frustrating, area of business.

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India Changes Law

In 2005, pharmaceutical companies were intrigued, when India—the country having the fourth largest economy in the world[1]—allowed patenting of drugs used for human therapy as compositions of matter. India has a rapidly growing economy with an increasing demand for better products, including pharmaceuticals. Moreover, India has an established legal system with roots in English common law and that uses English as its language of choice. Pharmaceutical companies viewed India's establishment of enforceable pharmaceutical patents as creating a coveted marketplace.[2]

[1] https://www.cia.gov/library/publications/the-world-factbook/rankorder/2001rank.html. Rank based on purchasing power parity; IMF and World Bank rank similarly.

[2] Though patenting drugs as compositions was allowed, treatment methods related to administering such drugs to humans continued to be unpatentable subject matter.

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The initial excitement, however, soon was watered down by the patent-defeating presence of Section 3(d) of the Patents (Amendment) Act, 2005.

Section 3(d): Hunting With the Hounds and Running With the Hare?

The Patents (Amendment) Act, 2005, eliminated Section 5 of the 1970s act, which described pharmaceuticals as unpatentable.[3] Drugs now could be patented in India. The 2005 amendments, however, added subsection 3(d), which states that the following were not inventions within the meaning of the amended act:

> 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.
>
> *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*.

Patents (Amendment) Act, 2005, Section 3(d), India (hereafter, simply referred to as Section 3(d)) (second and third emphasis added). Based on the ''Explanation,'' it becomes apparent that few compounds and compositions would qualify under the Indian patent law as new and patentable substance (as new chemical entities). Furthermore, consideration of the application of the above definition of ''derivatives'' to Cialis suggests that ''few'' might actually become ''zero.'' Before exploring how Section 3(d) has been applied, it may be interesting to follow its genesis and appreciate how this super-novelty and enablement statute came to being.

From Regulating Generic Drugs to Determining Patentability

Section 3(d), which makes it a super novelty or super enablement statute beyond what is required by the patents statutes in most of the rest of the world, originated in statutes regulating generic drugs. Section 3(d) is similar to the Directive 2004/27/EC of the European Parliament and Council of 31 March 2004, which provides guidelines for ''generic medicinal product'':

> generic medicinal product shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. *The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy*. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorized active substance must be supplied by the applicant.

2004 Official Journal of the European Union (L 136) 39 (emphasis supplied). The similarity between the italicized portion above and the portion entitled ''Explanation,'' under Section 3(d), is plainly apparent.

Thus, it appears that the incongruity apparent in Section 3(d) was created by importing a regulatory statute used to define and regulate generic drugs. In the regulatory context, the statute is drafted to broadly encompass compounds that may be regulated and approved as the generic drug of a reference product. However, using the same language to determine patentability creates patentability requirements that may run afoul of WTO's TRIPS requirements.[4]

Mere Discovery of New Forms of Known Substances

When Eli Lilly wanted to patent its Cialis erectile dysfunction drug in India, they faced a pre-grant opposition.[5] The structures of Cialis and the compound cited against it are shown below (on the next page, in print version).[6] Despite having a *methylenedioxyphenyl* moiety (shown within the square) where the prior art structure had a *hydrogen* or an *alkyl* group (shown within a circle), it was decided that Cialis was a derivative(!), under Section 3(d), of the cited generic, prior art structure.[7]

Therefore, based on the ''Cialis-test,'' it almost was impossible for any compound to be a new compound and avoid the demonstration of efficacy as required by the Section 3(d). This brings us to the second part of the threshold test for patentability of drug compositions in India: the requirement to demonstrate superior efficacy over the prior art compound.

Under the two-prong Section 3(d) attack, many pharmaceutical patents were invalidated, and applications rejected.[8, 9] Notable among them were, Eli Lilly's Cialis (a *derivative*), Novartis's Glivec (a *salt* of known compound), Bayer's Nexavar (a *derivative* of known ''quinazoline''), Roche's Tarceva (an isolated *polymorph*), and Gilead's Viread (a fumarate salt of a known compound).[10] Each of these compounds was held to be simply derived from a known compound. Section 3(d), therefore, mandated that to be patentable,

[3] Under deleted section 5, only methods or processes of manufacture of pharmaceuticals were patentable.

[4] Under TRIPS, a patent should be granted to any composition which is novel, includes an inventive step, and has industrial applicability.

[5] Chapter V, Section 25 of the Patents (Amendment) Act, 2005, India.

[6] http://www.i-mak.org/storage/Eli%20Lilly%20App%20No%2085-DEL-1995%20v%20Ajanta%20Pharma%20Ltd%202007.pdf.

[7] For the prior art structure and its uses, which appear unrelated to reducing blood pressure or treating erectile dysfunction, see, US 3,917,599.

[8] http://www.i-mak.org/pharma-patent-decisions/.

[9] As a result of refusal of patent grant by the Indian Patent Office, and invalidation by pre- and post-grant oppositions.

[10] See, http://www.i-mak.org/pharma-patent-decisions/.

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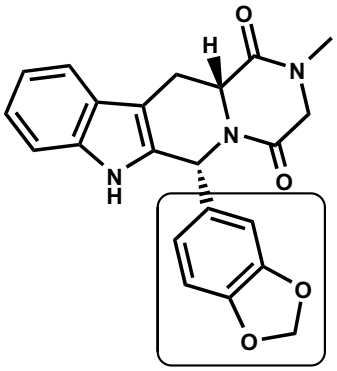
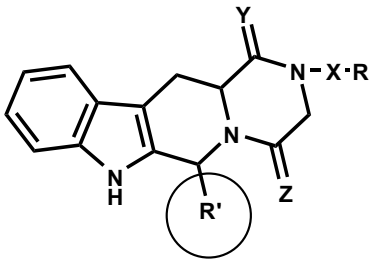


Cialis®



Generic prior art structure (R' is H or alkyl)

the applications claiming these compounds had to provide evidence of their comparative efficacy over the known compounds. Most applications were found to lack such comparative efficacy data. Thus, many concluded that the 2005 amendments had not really made drugs patentable in India.

A recent court decision, however, suggests that the conclusion that drugs continue to be unpatentable in India might be premature. The Madras High Court construed the comparative efficacy requirement in Section 3(d) to elucidate what was required to show that the claimed and prior art compounds ''differ significantly . . . [in] efficacy.''[11] An illuminating opposition proceeding where a patent for a pharmaceutical agent prevailed based on its significantly different efficacy further suggested that there is reason to hope that valid pharmaceutical patents may be obtained in India.[12] At the very least, after the initial chaos, clarity appears to finally be emerging in the area of Indian drug patenting.

''To Differ Significantly in Efficacy,'' What Does It Mean?

When Novartis applied for a patent for its blockbuster drug Glivec (imatinib *mesylate*) in India, it was rejected under Section 3(d). The patent office argued that imatinib was known, therefore, being a *salt*, its mesylate *salt* would be considered the same as imatinib (and be unpatentable) unless there was a showing of significant difference of efficacy over imatinib. The office disregarded enhanced solubility and bioavailabilty of the mesylate over imatinib as evidence of its significantly different efficacy over imatinib. Novartis challenged the patent office's decision in the Madras High Court. That court construed the meaning of efficacy as follows:

> Darland's Medical Dictionary defines the expression ''efficacy'' in the field of Pharmacology as ''the ability of a drug to produce the desired therapeutic effect'' and ''efficacy'' is independent of potency of the drug. Dictionary meaning of ''Therapeutic,'' is ''healing of disease—having a good effect on the body.'' Going by the meaning for the word ''efficacy'' and ''therapeutic'' extracted above, *what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease / having a good effect on the body*? In other words, the patent applicant is definitely aware as to what is the ''therapeutic effect'' of the drug for which he had already got a patent and *what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for*. Therefore it is a simple exercise of, though preceded by research,—we state—for any Patent applicant to place on record what is the therapeutic effect/efficacy of a known substance and what is the enhancement in that known efficacy.[13]

In doing so, the court agreed with the patent office that Glivec was unpatentable under Section 3(d).

The patent office further illustrated the meaning of ''*healing a disease/having a good effect on the body*'' in the opposition proceeding related to the patent covering Pegasys.[14] The patent claimed various polyethylene glycol conjugates of interferon-α (PEG-IFN) and preparative methods and compositions related to them. The application described *comparative data between PEG-IFN* and interferon-α (*IFN*). The data related to *in vitro* antiviral activity, anti-proliferative activity, and *in vivo* (in mice) immunogenicity and anti-tumor activity. In the opposition, it was first decided, as expected, that PEG-IFN was the derivative of a known compound, IFN, and implicated Section 3(d). But, most importantly, it was then concluded that, the experiments described proved there was indeed an enhancement in known efficacy (anti-viral and anti-tumor efficacy) of PEG-IFN over IFN. This decision was the first that demonstrated that indeed a compound might implicate Section 3(d) and yet be patentable by demonstrating comparative, therapeutic superiority over the corresponding prior art compound.

[11] Novartis v The Union of India, Madras High Court, 2007, http://www.i-mak.org/storage/Novartis%20v%20Union%20of%20India%20-%20Madras%20High%20Court%202007.pdf.

[12] Involving Roche's Indian patent covering Pegasys (corresponding to US 7,201,897). See, http://www.i-mak.org/storage/F%20Hoffmann%20La%20Roche%20Patent%20No%20198952%20v%20Wockhardt%20Ltd%20and%20Sankalp%20Rehabilitation%20Trust%202009.pdf.

[13] Section 13, page 52 of the court's opinion (emphasis supplied), http://www.i-mak.org/storage/Novartis%20v%20Union%20of%20India%20-%20Madras%20High%20Court%202007.pdf.

[14] Indian Patent No. 198952 (App. No. 1032/MAS/1997; corresponds to US 7,201,897).

While Novartis provided comparative solubility and bioavailability data between imatinib mesylate and imatinib itself, such data were not considered pertinent to efficacy. In a recent ruling, the intellectual property appellate board concluded that,

> [t]hese physical properties in a drug are important to formulate the active ingredients in solid dosage forms such as capsules, tablets, etc. but has no contribution to actual therapeutic effectiveness of the drug.[15]

Similarly, in a pre-grant opposition proceeding related to Boehringer Ingelheim's nevirapine hemihydrate, the claims were rejected.[16] The hemihydrate claimed was of a certain size, which, due to their solution stability, was useful for manufacturing nevirapine. But the adjudicating board concluded ''it was not shown that the therapeutic effect of nevirapine hemihydrate in aqueous solution is significantly enhanced over known forms of nevirapine.''

Can These Cases Be Explained?

Two things were apparent from the High Court's opinion and its application in the various opposition and patent office proceedings. If Section 3(d) is implicated—and it is very rare for it not to be—*first*, comparative data between the claimed compound and the known or prior art compound were required, and *second*, the comparative data should pertain to healing a disease/having a good effect on the body. *In vitro* and *in vivo* data that demonstrate comparative benefits of a treatment outcome (such as reduction in tumor mass or anti-viral activity in the relevant therapeutic areas) might be sufficient for the comparative efficacy analysis under Section 3(d). Improved stability or bioavailability of a composition of matter alone, however, might be insufficient if not directly correlated to improved therapy.[17] And, post-filing data are not acceptable under Indian Patent Law to demonstrate comparative therapeutic advantage.[18, 19]

TRIPS Compliance

While tunneling through the Section 3(d) barricade as described above, the legality of the section itself has been questioned and evaluated. As a member of the WTO, India is held to the intellectual property standards agreed upon by the WTO and TRIPS.[20] Under TRIPS, a patent may be granted to any composition which is novel, includes an inventive step, and has industrial applicability. Since pharmaceuticals possessing all three of the aforementioned still could fail the Section 3(d) test, it was questioned if it indeed was legal under the TRIPS.[21]

The Indian government formed a committee to study this question. In a report submitted recently, the committee concluded that, ''it would not be TRIPS compliant to limit granting of patents for pharmaceutical substance to New Chemical Entities [as defined by section 3(d)] only.''[22]

The Future of Indian Drug Patenting

The early stage of drug patenting in India has been clouded by the application of the Section 3(d). However, shafts of light are emerging through that cloud as standards of the comparative efficacy standards have been clarified in Novartis's Glivec related cases and applied to uphold Roche's patent for Pegasys. It also is possible that India may evaluate the TRIPS compatibility of the section and eliminate it or tone it down, either of which will further help drug patenting in India.

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[15] Page 189 of the order of the Intellectual Property Appellate Board passed on June 26, 2009, http://www.i-mak.org/storage/Gleevec%20IPAB%20decision%2026%20June%202009.pdf.

[16] http://www.i-mak.org/storage/pgopposition-Nevirapine%20hemihydrate.pdf%20.pdf.

[17] See, page 157-158, subsection xxi, entitled ''[w]hether enhanced efficacy and advantageous properties in a drug stand for the same,'' http://www.i-mak.org/storage/Gleevec%20IPAB%20decision%2026%20June%202009.pdf.

[18] See, page 153-154, subsection xvii, http://www.i-mak.org/storage/Gleevec%20IPAB%20decision%2026%20June%202009.pdf.

[19] If comparative testing is undertaken, there might be a duty to disclose the results in various countries, such as, e.g., the United States.

[20] The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), negotiated in the 1986-94 Uruguay Round, introduced intellectual property rules into the multilateral trading system for the first time.

[21] See, *e.g.*, http://www.novartis.com/downloads/about-novartis/india-glivec-patent-case-faq.pdf.

[22] http://ipindia.nic.in/ipr/patent/patents.htm (follow, Report of the Technical Expert Group on Patent Law Issues, page 8).

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