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The Patent Failure of Novartis with Gleevec, Note on Novartis v. Union of India Judgment

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The Indian Supreme Court's verdict on the Novartis patent application has garnered a lot of attention as having set a stringent standard of nonobviousness for patents. In India, this litigation is pitched as a battle between big pharma and health aid groups.

This recent saga at the Supreme Court relates to a patent application that was originally filed in 1998 for a cancer drug named Gleevec (or Glivec, in Europe). Gleevec is the beta crystalline form of imatinib mesylate, which is the salt form of the free base and is used to treat chronic myeloid leukemia, a form of cancer.[1] This application in India claimed priority from an earlier application filed in July 1997 in Switzerland.[2] The application was opposed in India on the basis that imatinib mesylate was anticipated by the earlier Novartis US patent No. 5521184. As a side note, Novartis's US application for the free base of Imatinib -which was the crystalline form —issued as a patent in the United States in 1996 owing to a 1993 filing date.[3] When after losing the mail-box dispute, India opened its doors to a transitional mail-box application facility, Novartis filed a patent application in India in 1996. Overall, Novartis had over 35 patents over this polymorphic form of Gleevec in different countries. The application was reviewed in India

[1] *See* Novartis AG v. Natco Pharma and Others, Controller of Patents and Designs, Application No. 1602/MAS/1998 (2005) (India), *available at* http://indiankanoon.org/doc/1352538/ [hereinafter "*Novartis v. Natco*"].

[2] *See* Indian Patent Application No. 1602/MAS/1998 (filed July 17, 1998) (published April 15, 2005) ("Crystal Modification of A.N.-Phenyt-2-Pyrimidineamine derivative, processes for its manufacture and its use").

[3] U.S. Patent No. 5,521,184 (filed Apr. 28, 1998) ("Pyrimidine derivatives and processes for the preparation thereof.").

in 2006 once India fully transitioned into a patent regime as required under the TRIPS agreement. Notably, even before the application was taken up by the patent office there were 5 pre-grant oppositions filed against the application!

In gist, the argument against Gleevec in India was that this application related to new form of a known substance. In pharmaceutical chemistry, a different crystalline form of the same chemical substance is called a polymorph, the patenting of which is specifically prohibited under § 3(d) in India unless it also results in *enhanced efficacy*.[4] § 3(d) of the Indian patent statute, the operative section reads as follows:

> 3. What are not inventions. - The following are not inventions within the meaning of this Act,
>
> …
>
> (d). the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.
>
> 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;

In gist, India does not allow the patenting of new forms of known substances unless it also results in enhanced efficacy. The assertion in India was that the salt form for which the patent application was filed inherently existed in the original crystalline form.[5] Considering the US patent as a prior art, the Patent Controller concluded that the application was obvious for

[4] *See* Andrew D. Bond, Roland Boese & Gautam R. Desiraju, *What Is a Polymorph? Aspirin as a Case Study*, AM. PHARM. REV., *available at* http://americanpharmaceuticalreview.com.

[5] *Novartis v. Natco, supra* note 165, ¶ 5.

covering a new form of a known substance under § 3(d) of the Patents (Amendment) Act of 2005.[6]

Soon Novartis pursued an appeal to the High Court of Chennai on the grounds that § 3(d) was unconstitutional and in violation of India's obligations under TRIPS.[7] The Chennai High Court established that § 3(d) was indeed Constitutional and within the scope of the TRIPS agreement based on the fact that the section deals with all technologies and does not limit itself to pharmaceutical innovations. The explanation to the section becomes applicable to pharmacology inventions and works to strengthen the understanding of the overarching test. The test, the court explained cast a duty on the patent applicant to prove that the discovery had resulted "enhancement of a known efficacy of that substance." The court added that the explanation creates a "deeming fiction that all derivatives of a known substance would be deemed to be the same substance unless it differs significantly in properties with regard to efficacy."[8] Thus, was born the higher standard of nonobviousness that India has embraced with such vigor. In its opinion, the Chennai High Court agreed with the patent office that Gleevec was an obvious improvement and that the applicant should prove *enhanced efficacy* by showing enhanced therapeutic efficacy in order to get a patent.[9] Interestingly, Novartis filed another

[6] Ashling O'Connor, *Activists Protest at Novartis's Patent Law Challenge*, TIMES (UK), Mar. 7, 2007, at 59; *see also* Patents (Amendment) Act, 2005, No. 15, § 3(d), Acts of Parliament, 2005 (India), http://www.wipo.int/wipolex/en/text.jsp?file_id=128116.

[7] Novartis AG and Anr v Union of India and Others (2007) 4 MLJ 1153.

[8] Novartis AG, *supra* note 170.

[9] *Id.* at 45, 49; *see* Shamnad Bhasheer & T. Prashant Reddy, *The "Efficacy" of Indian Patent Law: Ironing out the Creases in Section 3(d)* (2008) 5:2 SCRIPTed (discussing the efficacy requirement).

patent application for the alpha version of the same compound; that application was also denied.[10]

It was during this time that the government of India issued a notification constituting the Intellectual Property Appellate Board (IPAB), which is a tribunal with judicial powers under which all patent appeals were transferred.[11] It is important though to understand that, despite being a tribunal, the IPAB's judicial pronouncements have gained in reputation and stature over the years. Eventually, the Novartis patent application, like the other patent appeals, landed in the hands of the newly constituted IPAB on transfer from the High Court.[12] The IPAB alluded to the original 1993 Zimmerman Patent facilitated the formation of imatinib mesylate salt by reaction with "aliphatic sulfonic acids, such as methane -,ethane - or - 2-hydroxy ethane -sulfonic acid." Interestingly, the IPAB clarified when nonobviousness is evaluated for a pharmaceutically active substance, in particular, the application material would finally have to be evaluated to determine whether the compositions fall within the category of "not an invention under § 3(d) of the Act." This evaluation determined whether the new form/derivative of a known substance displayed significant enhancement in properties with regard to efficacy. Thus, the IPAB gave the impression that the § 3(d) analysis is tied to nonobviousness and not patent eligibility. In

[10] *See* Joe C. Mathew, *India Rejects Patent to Glivec's Second Variant*, BUS. STANDARD, Apr. 15, 2009, http://www.business-standard.com/india/news/india-rejects-patent-to-glivec/s-second-variant/355128/.

[11] *See* Ministry of Commerce & Industry, Notification No. 12/15/2006-IPR-III (Apr. 2, 2007) (India), http://ipindia.nic.in/ipr/patent/gazetteofindia_apr2007.pdf.

[12] *See* Notification No.12/15/2006-IPR-III, (2/4/2007), Ministry of Commerce & Industry, Government of India, *available at* http://ipindia.nic.in/ipr/patent/gazetteofindia_apr2007.pdf (last visited May 9, 2011).

considering Gleevec, the IPAB held that the increased bioavailability of the salt of imatinib (application material) and the increased solubility did not result in increased efficacy.

Novartis preferred an appeal to the Supreme Court in 2009, the same year that the IPAB upheld the rejection of Gleevec by the Controller. The Supreme Court considered whether an invention that clears all of the requirements for an invention can be denied on the ground that § 3(d) puts it out of the category of "invention"?[13] The manner of phrasing the question in itself suggests that § 3 is not a threshold question in India. That is, one gets the feeling that whether an application material falls within the category excluded under § 3 is determined only for inventions that cross the § 2 requirements of utility, novelty and nonobviousness. This view is further bolstered by the statement elsewhere by the Supreme Court that "in case of chemicals and especially pharmaceuticals … [of] a new form of a known substance with known efficacy, [] the subject product must pass, in addition to clauses (j) and (ja) of section 2(1), the test of enhanced efficacy as provided in section 3(d) read with its explanation." That said, elsewhere the court, in denying that § 3 is not a provision *ex majore cautela*, adds that the vital distinction is between the concepts of invention and patentability. So, the conclusion perhaps is that § 3 is akin to patentability question although in practice in India, it is tagged with the nonobviousness question.

As for the specific constituents of the § 3(d) requirements, the Supreme Court clarified that the term efficacy relates to "therapeutic efficacy." The court then went on to discuss the test or parameters for providing such efficacy noting that such proof shall be weighed on strict and narrow standards. In the case of pharmaceutical compounds, the Court noted external and internal factors should clearly demonstrate therapeutic efficacy and it should be specifically

[13] Natco Pharma Ltd., v. Union of India, & Otrs, Indian Supreme Court, Civil Appeal Nos. 2706-2716 OF 2013

claimed and established by research data. Thus, "the mere change of form with properties inherent to that form would not qualify as "enhancement of efficacy" of a known substance."

As for the patent itself, the court adopted a stance similar to the Controller of patents and the IPAB to hold that imatinib mesylate is represented entirely by the Zimmermann patent. It added that after the Zimmermann patent issued, Novartis applied for, and obtained patents on different forms of the substance. But, no application was made on imatinib mesylate on the non-crystalline form. The court concluded that it is because imatinib mesylate is fully a part of the Zimmermann patent and does not call for a separate patent and thus, denied the patent.

Notably, the interest and role of non-governmental organizations in India in access issues as far as intellectual property is concerned is remarkable and distinguished. Further, the country's interest in hearing and dispensing intellectual property issues has also become notable. The Novartis litigation has showcased India's interest and ability as far as pharmaceutical patents are concerned. This case reinforces the suspicions for the need of a higher bar to get a patent issued in India. It also proves that the power of lobby groups notwithstanding, businesses needs a dose of local reality especially in countries in India. It must take exceptionally bad market assessment to sell a drug for approximately $ 2400 for a month's supply (against a cost of $ 160 for the same from a generic manufacturer) in a country where the per capita income is estimated at a low $ 1 to $ 10 per month for a vast majority of the population. To give a perspective, an Indian employee who earns $ 2400 per month would consider himself very well-employed. In fact, in the lower middle class (forming about 300 to 400 million people), one would be considered agreeably employed if they earned $ 2400 in a year. And, big pharma cannot hope to erase away this ground reality with its lobby power.

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