IP Hotline

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NOVARTIS INDIAN SUPREME COURT JUDGMENT: WHAT IS EFFICACY FOR PHARMACEUTICAL INVENTION ?

The Indian Supreme Court (SC) on April 1, 2013 delivered a landmark judgment rejecting Novartis's 1998 Indian patent application for beta-crystalline form of Imatinib Mesylate, a drug used to treat chronic myeloid leukemia (CML), a type of blood cancer marketed under the names "Glivec"or "Gleevec". This also ended Novartis eight year battle with various Indian legal forums to get its drug patented.

The SC for the first time has interpreted Section 3 (d) of the Indian Patent Act, 1970 (Act), which attempts to curtail ever-greening of patent[1]. The SC in its 112 page judgment traced the history of Indian patent law starting from the Justice Tek Chand committee report, 1949 to the 2005 amendment of Act, the SC laid particular emphasis on (i) Justice Ayyangar report on Patent Law Revision, 1959 (the 1970 Act was enacted based on the recommendations in this report) (ii) effect on the Indian Pharmaceutical industry due to the changes in the Patent Law (the SC looked at statistics relating to Market share of Indian Pharmaceutical companies vs. MNC pharmaceutical companies pre 1970 and post 1970) (iii) why pharmaceutical, chemical and food product patents were not permitted till 2005, (iv) how India had to retrospectively introduce product patent regime after having lost at the WTO (World Trade Organization), wherein the WTO panel and the appellate body had ruled that India had failed to meet its TRIPS (Trade Related Aspects of Intellectual Property Rights) obligations (v) relevant provisions of the TRIPS agreement and flexibilities under the Doha declaration (vi) the facts and the background leading to introduction of Section 3 (d) including parliamentary debates and the letters received from various organizations like WHO (World Health Organization) and UNAIDS . After extensive deliberation on these points the SC proceeded to apply the law to the facts of Novartis patent application.

In this update, we have discussed the specific facts discussed by the SC and its findings and have also commented upon other observations that will have bearing on the patent prosecution in India.

BACKGROUND
The facts of the case have been summarized in the table below.

	Fact and Comments
July 17, 1998	Novartis filed Indian patent application for the beta-crystalline form of Imatinib Mesylate ("**Product**"). At that time the Act allowed acceptance of product patent applications as per "mail box" process and the same was contemplated to be examined post January 1, 2005 once India introduced product patent regime. This was in line with TRIPS requirement.
1998 – Jan 1,2005	The application was kept in mailbox as required under TRIPS and the Act.
2002 – 2003	In the meantime, Novartis applied for and was granted exclusive marketing rights (EMR) in relation to Product under the then existing Section 24A of the Act, which also was in line with TRIPS.
Jan 1, 2005	India introduced product patent regime and simultaneously amended Section 3(d) of the Act[2]. Section 3(d) disallows the patenting of a new variant of an already known substance unless such new form has significant efficacy over the older version. This was introduced with a view to prevent ever-greening and granting of frivolous patents.
2005	Novartis patent application before it was taken up for examination attracted five pre-grant opposition filed by Cancer Patients Aid Association, NATCO Pharma, Cipla, Ranbaxy Laboratories and Hetro Drugs (Opponents).
Jan 25, 2006	Asst. Controller of Patents upheld the pre-grant oppositions and rejected Novartis' patent application ("**Controller Order**") on the grounds that the application lacked novelty, was obvious and was not an invention in view of Section 3(d) of the Act. Controller held that the Product was a new version of an older molecule that Novartis first patented in 1993 and the increment in efficacy is not substantial enough to receive the grant of a patent.

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May 2006	Since the appellate authority Intellectual Property Appellate Board (IPAB) under the Act was not established, Novartis filed writ petitions before the Madras High Court against the Union of India, the Controller General of Patents & Designs ("**Controller"**), Opponents. Novartis contended that (i) the Controller erred in interpreting the enhanced efficacy standard imbibed in Section 3(d) with regard to Product, (ii) Section 3(d) was vague, ambiguous and contrary to the requirements of TRIPs and that it violated Article 14 (right to equality) of the Constitution of India, (iii) the Controller disregarded the in-house laboratory test performed by Novartis' scientists on rats to show that a 30% increase in bioavailability between imatinib and imatinib mesylate was adequate to meet up the "enhanced efficacy" benchmark of section 3(d).
April 2007	The Central Government issued a notification under Section 117G of the Act whereby all appeals from the order of Controller, pending before the High Court, were transferred to the IPAB set up in Madras. Therefore, the Madras High Court transferred the appeal from the Controller's order rejecting patent to the IPAB. However, the Madras High Court, reserved the right to pronounce its judgment on the issue of the constitutional validity of Section 3(d) of the Act.
August 6, 2007	The Madras High Court held that Section 3(d) does not violate Article 14 (right to equality) of the Constitution of India[3]. This order was not appealed further by Novartis.
June 26, 2009	The IPAB reversed the decision of the Assistant Controller on the issues of anticipation and obviousness. However, the IPAB held that the subject matter of the patent application was barred from patentability under Section 3 (d) of the Act and therefore rejected the patent. However, it allowed the process patent for the Product.
August 11, 2009	Against the order of the IPAB Novartis filed a special leave petition (SLP) under Article 136 of the Indian Constitution in the Indian Supreme Court.
April 1, 2013	Order of the Supreme Court

The SC had made an exception and admitted the SLP side-stepping the jurisdiction of the Madras High Court, in view of the importance of the case and the number of seminal issues that were involved in the case. The SC noted that this was an exception and any attempt directly challenging an IPAB order before the SC side-stepping the High Court was strongly discouraged.

We have examined below each concept discussed by the Supreme Court:

Invention vs. Patentability

A subject matter in order to get a patent under the Act has to pass the test of Invention and Patentability, both being distinct concepts.

In order for a subject matter to pass the test of Invention it must satisfy the following conditions as laid down under Section 2(1) (j) and Section 2(1) (ja) of the Act

i. It must be "new";

ii. It must be "capable of being made or used in an industry"

iii. It must have inventive step

a. entails technical advance over existing knowledge;

Or

b. has an economic significance

And

c. makes the invention not obvious to a person skilled in the art.

Once a product or a process has passed the test of Invention it also has to pass the test of Patentability. A subject matter passes the test of Patentability if it has not been specifically excluded from Patentability under the Act. Section 3 and Section 4 of the Act list down subject matter which is not patentable.

The Invention

The invention as claimed in the patent application was the beta-crystalline form of Imatinib Mesylate. This was a derivative of the free base form called Imatinib disclosed vide example 21 of a patent application filed by Novartis in US on April 2, 1993 (**Zimmermann patent**).

According to Novartis the invention as claimed in the patent application involved two inventions. The

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first invention involved selecting example 21 out of the 37 examples given in the Zimmermann patent and then choosing methane sulfonic acid to produce the methane sulfonic acid addition salt of the free base Imatinib, called Imatinib Mesylate. The second invention involved making Imatinib Mesylate suitable for oral administration, which resulted in creation of the present invention in question i.e. beta-crystalline form of Imatinib Mesylate.

According to the opponents the Zimmermann Patent in addition to the Imatinib also disclosed Imatinib Mesylate. Thus, there was only one invention, which is making Imatinib Mesylate suitable for oral administration.

Imatinib vs. Imatinib Mesylate

In order to verify the claim of Novartis that its application involved two inventions, it was essential for the SC to determine whether the Zimmermann patent in addition to Imatinib disclosed Imatinib Mesylate. If the answer was in the affirmative then Novartis claim of two inventions was incorrect because if the Zimmermann patent did disclose Imatinib Mesylate then the first invention i.e. Imatinib Mesylate would not qualify as an invention under Section 2 (1) (j) and 2(1) (ja) of the Act, as it will not be a technical advance over the existing knowledge.

The SC referred to the following disclosures in the Zimmermann patent and developments surrounding the Zimmermann patent:

- "may form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids…"
- "any reference to the free compounds should be understood as including the corresponding salts, where appropriate and expedient."
- "The invention relates also to a method of treating warm-blooded animals suffering from a tumoral disease, which comprises administering to warm blooded animals requiring such treatment an effective, tumour-inhibiting amount of a compound of formula I or of a pharmaceutically acceptable salt thereof.."
- On April 9, 1998 Novartis had filed for a New Drug Application to obtain a Food and Drug Administration (FDA) marketing approval in the US for Gleevec with which it had furnished information that the active ingredient of the drug was Imatinib Mesylate and the same was covered by the Zimmerman patent.
- The FDA approval for the Drug Gleevac (Imatinib Mesylate) was granted on May 10, 2001 and was commercially launched in the market much before the grant of the patent for beta crystalline form of Imatinib Mesylate
- Novartis had sent a legal notice to Natco Pharma in the UK to stop selling their drug called VEENAT consisting of Imatinib Mesylate because it was infringing there European equivalent of the Zimmermann Patent.
- Novartis patent application in the US for beta crystalline form of Imatinib Mesylate was rejected by the US examiner. Novartis appealed the examiners decision to the Board of Patent Appeals and Interference (Board). In its decision the Board had observed that the "specification of the Zimmermann patent teaches any person skilled in the art how to use imatinib, or a pharmaceutically acceptable salt thereof"
- Novartis had not filed for a separate patent for Imatinib Mesylate
- Two articles published in Cancer Research and Nature Medicine in 1996 authored by Jurg Zimmermann (Inventor in the Zimmermann patent) had a detailed discussion about the anti-tumoral properties of Imatinib and its methanesulfonate salt i.e. Imatinib Mesylate.

Based on the above facts the SC held that the Zimmerman patent did disclose Imatinib Mesylate as well as its pharmacological properties. Thus, Novartis claim of its invention involving two inventions failed and it consisted of only one invention, which is making Imatinib Mesylate suitable for oral administration which had resulted in the beta crystalline form of Imatinib Mesylate. This finding of the SC was also essential as a precursor to determine, the known substance that beta crystalline form of Imatinib Mesylate should be compared with for establishing enhanced efficacy under Section 3 (d).

Patentability Analysis – Section 3 (d)

The main argument of the opponents was that the Product was not patentable under Section 3 (d)..

Section 3 (d) reads as:

[(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 order to pass the bar of Section 3(d) it was required to be proved that the Product has enhanced efficacy over the known form of the subject matter.

What was the known substance?

After examining the pleadings and expert affidavits, the SC observed that Novartis' argument was that the known substance was Imatinib as disclosed in Zimmerman patent from which beta-crystalline form of Imatinib Mesylate was derived and that the substance immediately preceding beta crystalline form of Imatinib Mesylate was Imatinib and not Imatinib Mesylate as the Zimmerman patent did not disclose Imatinib Mesylate. The SC rejected this argument because it had made a finding that the Zimmerman patent did disclose Imatinib Mesylate. Further, the SC also rejected this argument in view of the fact that this was in contrast to the oral and written submissions of Novartis before the SC, wherein Novartis had argued that its invention involved two stages removed from Imatinib in free base, and the substance immediately preceding the subject product is Imatinib Mesylate.

Hence, the SC concluded that the known substance was Imatinib Mesylate from which beta-crystalline form of Imatinib Mesylate was derived.

Efficacy under Section 3(d)

Since the term "efficacy" is not defined in the Act, the SC referred to the Oxford Dictionary and observed that Efficacy means "the ability to produce a desired or intended result". Accordingly the SC observed that the test of efficacy depends "upon the function, utility or the purpose of the product under consideration". Therefore, the SC held that in case of medicines, whose function is to cure disease, the test of efficacy can only be "therapeutic efficacy".

In relation to "enhanced efficacy", the SC held that the parameters for proving enhanced therapeutic efficacy especially in case of medicines should receive a narrow and a strict interpretation. To support this interpretation SC relied on (i) the explanation to Section 3 (d) which requires derivatives to "differ significantly in properties with regard to efficacy", so not all advantageous and beneficial parameters would amount to enhancement of efficacy; and (ii) the main text of Section 3 (d) which states "enhancement of known efficacy". The SC held that the new form of a known substance has to have significant advantageous and beneficial properties over known substance in order to pass the bar of enhanced therapeutic efficacy under Section 3 (d).

However, the SC pointed out that just because the word efficacy has to be given a strict interpretation under Section 3 (d) that does not in any way mean that it bars all incremental inventions of chemical and pharmaceutical substances. Essentially Section 3 (d) provides a bar that incremental inventions of chemical and pharmaceutical substances need to pass in order to be patentable.

Efficacy of beta-crystalline form of Imatinib Mesylate

As discussed above the SC had concluded that the known substance was Imatinib Mesylate and not free base Imatinib. However, all the evidence submitted by Novartis compared the efficacy of Product with that of Imatinib, there was no evidence provided by Novartis which compared the efficacy of the Product with that of Imatinib Mesylate.

However, SC went on to examine the expert affidavits submitted by Novartis according to which the following properties exhibited by the Product demonstrated its enhanced efficacy over Imatinib:

(1) More beneficial flow properties

(2) Better thermodynamic stability

(3) Lower hygroscopicity

(4) 30 % increase in bio-availability

The SC held that the first three properties of the Product related to improving processability and storage, thus they did not in any way demonstrate enhancement of therapeutic efficacy over Imatinib Mesylate as required to pass the test of Section 3(d). The SC came to this conclusion even though the affidavits submitted by Novartis compared the Product over Imatinib.

The SC after this was left with 30 % increase in bio-availability, with regard to this the SC held that increase in bioavailability could lead to enhancement of efficacy but it has to be specifically claimed and established by research data. In this case the SC did not find any research data to this effect other than the submission of the counsel and material "to indicate that the beta-crystalline form of Imatinib Mesylate will produce an enhanced or superior efficacy (therapeutic) on molecular basis than that could be achieved with Imatinib free base in vivo animal".

In view of the above findings the SC held and concluded that Novartis claim for the Product failed both the test of invention and patentability under Section 2(1) (j), Section 2(1) (ja) and Section 3 (d) of the Act.

ANALYSIS

The SC did not have any guidance from the Act in interpreting Section 3 (d). Hence it referred to the parliamentary debates and the circumstances surrounding enactment of Section 3 (d) to a great extent to give a purposive interpretation. Further, considering that Section 3 (d) is very unique to India, it was very important both for the pharma industry and the patent office to have guidance on its interpretation . Though SC has attempted to clarify certain aspects, some issues are still open.

One debate that was laid to rest was whether efficacy under Section 3 (d) for pharmaceuticals is therapeutic efficacy. The SC has made it clear that efficacy for a pharmaceuticals refers to only therapeutic efficacy. The SC ruled that enhanced therapeutic efficacy should be interpreted strictly and properties such as improving storage, processability and inherent pharmacological properties do not amount to enhancement of therapeutic efficacy.

Thus, there is some guidance on parameters that do not amount to enhanced therapeutic efficacy but

there is no guidance as to what parameters amount to therapeutic efficacy. The SC does state that increase in bioavailability can amount to enhancement of therapeutic efficacy if established by research data. One can take a cue from this that appropriate research data needs to be provided to show enhancement of therapeutic efficacy but the question what kind of research data would suffice to meet this requirement has been kept open. Guidance on these aspects would have been of immense help to the various stakeholders even though the court did not have to rule on these aspects to decide the present case.

Another important aspect highlighted in the judgment is the need to identify exact prior substance against which the invention should be compared. The practical difficulty in obtaining comparative data will need to be resolved once it is clear as to the nature of data that will be accepted to prove therapeutic efficacy. This clarity is likely to come in through the orders of the controllers and IPAB in similar matters.

One vexing issue prior to this judgment faced by patent applicants was whether the evidence required to establish enhancement of therapeutic efficacy should be included in the specification or external evidence would suffice. This issue seems to have been laid to rest, since the SC has relied on external evidence i.e. expert affidavits to decide enhancement of efficacy in this case.

The SC has clarified that the judgment in this case should not be understood to mean that Section 3(d) bars all incremental inventions of chemical and pharmaceutical substances. However, the bar that has been set by the SC to surpass the hurdle of Section 3 (d) is very high.

As a matter of principle if prevention of ever-greening of patent is the real mischief that is sought to be remedied by Section 3(d), then it is important to take into consideration whether prior substance was indeed commercialized. The reason being often the prior substance is in free base form and not the salt form. A free base form generally cannot be administered to humans whereas a salt form can be administered thus the free base form cannot be commercialized. In a drug discovery cycle it is the free base form which is discovered first, thus generally phrama companies file for a patent for the free base form encompassing all salt forms in order not to lose the priority, at this stage the pharma companies are not generally aware as to what salt form of the free base would have most therapeutic efficacy. This discovery is generally made after conducting extensive human or animal clinical trials.

This point becomes very important because if a salt form cannot be claimed separately due to Section 3 (d). Then in order to stop a patent infringer from using the salt form of its drug, the pharmaceutical company has to rely on its patent covering its free base form. However, the first argument raised by the defendant in its counter claim is that the salt form is not covered under the free base patent and a broad claim which claims all salt forms is not enabling. Thus, the defendant is not infringing the patent. This issue is sub judice in the Merck v/s. Glenmark suit before the Delhi High Court.

Hence, this is a big dilemma for pharmaceutical companies and needs to be addressed. The purpose of Section 3(d) is to prevent pharmaceutical companies from extending their period of monopoly i.e. evergreening of patents but it should not stifle inventions. Hence, the parliament and judiciary should revisit the provision so that it is only the new form of the known “commercialized” substance may not be granted patent unless enhanced therapeutic efficacy is shown.

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http://www.nishithdesai.com/Pharma-update/Pharma-update-Nov15-2003.htm

[2] http://www.nishithdesai.com/Pharma-update/2007/Pharma-update-Aug1007.htm

[3] http://www.nishithdesai.com/Pharma-update/2007/Pharma-update-Aug1007.htm