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What should we learn from the Novartis judgment?

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On 1 April 2013, the Supreme Court of India delivered a landmark judgment in which the Court upheld the decision of the Indian Patent Office to reject Novartis's patent application on imatinib mesylate, a life-saving medicine used for the treatment of chronic myeloid leukaemia (CML). The judgment put an end to a series of litigations between Novartis, generic drug companies and the Cancer Patient Aid Association (CPAA).

Novartis had obtained the marketing approval from the US Food and Drug Administration (USFDA) in 2001 for the treatment of CML. It started marketing the medicine under two brandnames, Gleevec or Glivec. In India Novartis started marketing the medicine in 2002 at a price that would entail an expenditure of $2,500 per person per month.

However, during the same year Natco, an Indian generic drug company, started marketing the generic version of imatinib mesylate at less than a tenth of the originator's price. This move by Natco prompted another five generic companies to develop the generic version of imatinib mesylate. The Supreme Court decision now ensures the supply of imatinib mesylate from the generic companies within a price range of $100-150 per month.

Apart from ensuring an uninterrupted supply of the generic version of imatinib mesylate, the decision of the Court is an eye-opener for everyone regarding the greedy practices of multinational pharmaceutical corporations, which put profits above people's health. Further, it underlines the importance of curbing the patenting of a known substance by using the existing flexibilities in the World Trade Organisation (WTO)'s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).

The history of imatinib mesylate

Imatinib mesylate represents a new pathway in cancer treatment known as targeted therapies. Generally speaking, the treatment targets the

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affected cells without harming other cells. Imatinib mesylate targets the activity of a protein known as BCR-ABL which leads to CML. The basic research which led to the identification of the protein goes back to the early 1960s. However, it was a team of researchers led by Dr Brian Druker which developed the drug.

According to Druker, the entire research was primarily driven to meet the needs of CML patients and he had to lobby Novartis to invest money in the development of imatinib mesylate. He writes: 'I was caring for patients in my clinic with CML who had no treatment options remaining. I became their voice, lobbying my remaining contacts at Novartis to move this project forward. Ultimately, we prevailed.'

This polite statement by Druker is confirmed by Dr Arnold S Relman writing in the *Journal of the American Medical Association*: 'Novartis was not "the innovative force". Not only was all the basic research done in academic institutions, but so were the initial clinical investigations that showed [the compound] STI 571 to be specifically effective against CML cells in vitro and in vivo. In fact, it took a few years for Brian Druker, the investigator most responsible for these latter studies, to convince Novartis that it should invest in a crash programme to develop Gleevec and to undertake large-scale clinical trials.'

James Love of the NGO Knowledge Ecology International points out that the cost incurred by Novartis for the research and development (R&D) of imatinib mesylate is not very high. He cites the following facts to show the low expenses for the development of imatinib mesylate compared with the R&D cost of other medicines. According to Love, imatinib mesylate is designated as an orphan drug and this makes Novartis eligible for a tax credit to defray 50% of costs of clinical trials. Further, the approval letter for imatinib mesylate shows that the number of patients enrolled for the clinical trials was only 1,027, against the normal average of 2,667 for other medicines. Imatinib mesylate also obtained an accelerated approval in about three years compared with 5-7 years in the case of other medicines. The clinical trial was started in June 1998 and the USFDA provided the marketing approval on 20 May 2001.

However, after the marketing approval Novartis abused its patent monopoly and sold the medicine at an exorbitant rate. The sales turnover of imatinib mesylate in 2012 was around $4.68 billion. Novartis has recovered far more than the tiny investment it made in R&D for imatinib mesylate.

Novartis used different strategies to maintain the abuse of monopoly. It filed patents for the beta crystalline form of imatinib mesylate in many developing countries and sued generic companies. It financed patients groups to sue the government of Argentina to include imatinib mesylate as part of the state healthcare programme. In South Korea Novartis used political pressure to prevent the issuance of a compulsory licence on imatinib mesylate. To ease the criticism of the high prices, Novartis introduced a patient assistance programme known as the Glivec International Patient Assistance Programme (GIPAP). However, Dr Purvish Parekh of the Tata Cancer Hospital in Mumbai, India, filed an affidavit in 2007 with the High Court of Madras stating that Novartis misused GIPAP for post-marketing surveillance and further clinical trials.

Disappointed with the excessive price, Druker wrote in 2007: 'The price at which imatinib has been offered for sale by Novartis around the world has caused me considerable discomfort. Pharmaceutical companies that have invested in the development of medicines should achieve a return on their investments. But this does not mean the abuse of these exclusive rights by excessive prices and seeking patents over minor changes to extend monopoly prices. This goes against the spirit of the patent system and is not justified given the vital investments made by the public sector over decades that make the discovery of these medicines possible.'

The litigation

The litigation on imatinib mesylate started in 2003 in India. It took almost 10 years before a final answer was obtained from the Supreme Court, the highest judicial authority in India. Theoretically speaking, Novartis can file a review petition at the Supreme Court but legal experts believe there is little chance of overturning the present decision.

After obtaining marketing approval for imatinib

mesylate in India in 2002, Novartis applied for exclusive marketing right (EMR) in the country. Under the TRIPS Agreement, a developing country using the transition period for the introduction of a product patent regime should accept product patent applications during the transition period through what is known as the 'mailbox' facility. It should also provide EMR as an interim arrangement till the introduction of the product patent regime. The EMR will be granted on satisfaction of two conditions: first, patent protection and marketing approval in a foreign country, and, second, marketing approval in the country where the mailbox application is filed. After the introduction of product patent protection, the application would be examined as per the patentability criteria. Novartis obtained EMR in November 2003 for imatinib mesylate.

Novartis's EMR was challenged by Natco at the Delhi High Court primarily on the ground that imatinib mesylate was invented prior to 1995 and therefore not eligible for EMR under the Indian law. The Indian Patents Act clearly mentioned that EMR should be given only to those inventions claiming identical article or substance in a convention country on or after 1 January 1995. According to Natco, the invention mentioned in the 1998 application filed in India had already been disclosed through another patent application filed in the US in 1994, known as the Zimmermann patent. While Natco's writ petition was pending in the Delhi High Court, Novartis approached the Mumbai High Court seeking injunctions against Natco and its distributors to prevent the marketing of the generic version of imatinib mesylate. These litigations became redundant in 2005 due to the amendment of the Patents Act to introduce product patent protection.

Using the pre-grant opposition provision of the Patents Act, generic companies including Natco and the CPAA challenged the patent application of Novartis on imatinib mesylate. In January 2006 the Patent Office rejected the application, citing the absence of novelty and inventive step and the newly amended Section 3(d) of the Patents Act, which is supposed to curb the patenting of known substances.

Novartis challenged the decision of the Patent Office at the Madras High Court. It also challenged the constitutional validity of Section 3(d) and the compliance of the provision with the TRIPS Agreement through two writ petitions. Eventually the petition challenging the decision of the Patent Office was transferred to the Intellectual Property Appellate Board (IPAB). The Madras High Court heard and rejected the other two petitions. Novartis decided not to appeal against the decision of the Madras High Court.

The IPAB also rejected the patent application of Novartis but only on the ground of Section 3(d) of the Patents Act, and held that the application satisfied novelty and eligibility criteria under the Patents Act. Novartis approached the Supreme Court against this decision. At the same time Natco and the CPAA also approached the Supreme Court challenging the findings of the IPAB, which rejected the findings of the Patent Office on lack of novelty and inventive step in Novartis's patent application.

The Supreme Court on Novartis's greed

There were thus two questions which came up before the Supreme Court. The first concerned the legal validity of the IPAB decision which rejected Novartis's claim for patent protection on the beta crystalline form of imatinib mesylate under Section 3(d) of the Patents Act. The IPAB accepted Novartis's claim on novelty and inventive step but rejected the patent under Section 3(d). According to Section 3(d), a patent on a known substance cannot be granted unless there is a significant enhancement in the known efficacy. Further, as per the explanation of Section 3(d), '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.'

The second question which the Supreme Court had to consider was Natco's and the CPAA's legal challenges on the IPAB's decision to accept the argument of Novartis with regard to novelty and inventive step on the beta crystalline form of imatinib mesylate. As mentioned above, Novartis could not rely on the patent application filed in developed countries in 1994 known as

the Zimmermann patent, because there was no product patent protection in India at this time and the TRIPS Agreement only came into force in 1995. However, realising the market potential, it filed a patent application in India in 1998 seeking priority from a patent application filed in 1997 in Switzerland. Natco and the CPAA argued that the invention claimed in the 1998 application, i.e., the beta crystalline form of imatinib mesylate, was fully disclosed in the 1994 patent application. Further, making a beta crystalline form of salt from the imatinib molecule is obvious to a person skilled in the art and therefore does not satisfy the requirement of inventive step. Even though the Patent Office had accepted these arguments, the IPAB rejected them and denied Novartis's application only on one ground under Section 3(d).

At the Supreme Court, Novartis came up with a brand new argument which was not mentioned in its patent application filed in 1998. Novartis argued that the invention mentioned in the 1994 patent application was only the imatinib freebase and that two more inventive steps were required to reach the beta crystalline form of imatinib mesylate. The first inventive step was the development of salt from imatinib freebases and the salt was known as imatinib mesylate. The second inventive step was the development of the beta crystalline form of imatinib mesylate from imatinib mesylate. According to Novartis, the Zimmermann patent did not disclose these two inventive steps and therefore did not cover the beta crystalline form of imatinib mesylate claimed in its 1998 patent application.

On the issue of whether imatinib mesylate, i.e., the salt form, is disclosed in the Zimmermann patent, the Court clearly brought out the evidence to show that the Zimmermann patent covers not only the imatinib freebase but also the salt form of imatinib. Towards this purpose the Court found the following points.

The Court found the following statement in the Zimmermann patent, which clearly covers both freebase and salt of imatinib: 'Owing to the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification of the novel compounds or for the identification thereof, hereinbefore and hereinafter any reference to the free compounds should be understood as including the corresponding salts, where appropriate and expedient.'

The Court further found that Novartis filed the patent application for the beta crystalline form of imatinib mesylate in the US on 18 January 2000. The US patent was granted only after five and a half years, on 17 May 2005, following an order of the US Appellate Court dated 23 November 2003. The US Patent and Trademark Office (USPTO) had initially refused the patent application. The Court found out that Novartis launched the medicine in the market much earlier on the basis of the Zimmermann patent and declared to the USFDA that the Zimmermann patent covers 'the composition, formulation, and/or method of use of imatinib mesylate'.

Further, the Court also found that Novartis applied for extension of the term of the Zimmermann patent immediately after obtaining the marketing approval for imatinib mesylate. According to the Court, 'this application leaves no room for doubt that imatinib mesylate, marketed under the name Gleevec, was submitted for drug approval as covered by the Zimmermann patent'.

The Court also cited the fact that Novartis successfully prevented Natco from marketing its generic version of imatinib mesylate in the UK on the basis of the Zimmermann patent. The Court quoted from the US Board of Patent Appeals decision rejecting the USPTO order of refusing a patent for the beta crystalline form of imatinib mesylate. The Board of Appeals allowed the patent claim on the beta crystalline form but stated: 'In claim 23, Zimmermann recites imatinib, a specific compound within the scope of formula I, or a pharmaceutically acceptable salt thereof. In light of 35 U.S.C. 282, therefore, we may presume that the specification of the Zimmermann patent teaches any person skilled in the art how to use imatinib, or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition for treating tumours or in a method of treating warm-blooded animals suffering from a tumoral disease.'

The Court clearly stated: 'That imatinib mesylate is fully part of the Zimmermann patent is also borne out from another circumstance. It may be noted that after the Zimmermann patent, the

appellant applied for, and in several cases obtained, patent in the US not only for the beta and alpha crystalline forms of imatinib mesylate, but also for imatinib in a number of different forms. The appellant, however, never asked for any patent for imatinib mesylate in non-crystalline form, for the simple reason that it had always maintained that imatinib mesylate is fully a part of the Zimmermann patent and does not call for any separate patent.'

To support its argument regarding the non-coverage of the beta crystalline form of imatinib mesylate in the Zimmermann patent, Novartis argued that there is a difference between coverage and disclosure in a patent application. According to Novartis, the coverage of a patent application is different from the scope of disclosure of the patent. In simple terms it means that the absence of novelty or inventive step can be attributed to the steps involved in making the beta crystalline form of imatinib mesylate only if there is a complete disclosure in the Zimmermann patent.

Rejecting that argument, the Court said: 'The dichotomy that is sought to be drawn between coverage or claim on the one hand and disclosure or enablement or teaching in a patent on the other hand, seems to strike at the very root of the rationale of the law of patent. Under the scheme of patent, a monopoly is granted to a private individual in exchange of the invention being made public so that, at the end of the patent term, the invention may belong to the people at large who may be benefited by it. To say that the coverage in a patent might go much beyond the disclosure thus seems to negate the fundamental rule underlying the grant of patents.'

The Court further stated: 'We would like to say that in this country the law of patent, after the introduction of product patent for all kinds of substances in the patent regime, is in its infancy. We certainly do not wish the law of patent in this country to develop on lines where there may be a vast gap between the coverage and the disclosure under the patent; where the scope of the patent is determined not on the intrinsic worth of the invention but by the artful drafting of its claims by skilful lawyers, and where patents are traded as a commodity not for production and marketing of the patented products but to search for someone who may be sued for infringement of the patent.'

The Court did not examine whether transforming imatinib mesylate into the beta crystalline form of imatinib mesylate satisfies the inventive-step criterion. According to the Court, there was no need to examine that because the beta crystalline form of imatinib mesylate is a polymorph and directly attracts Section 3(d) of the Patents Act, which checks the patenting of known substances.

Novartis also made two arguments before the Court against the application of Section 3(d) to evaluate its patent application on the beta crystalline form of imatinib mesylate. Firstly, Novartis argued that Section 3(d) is a provision of abundant caution and does not apply to inventions which satisfy basic patentability criteria of novelty, inventive step and industrial application. Secondly, Novartis argued that since there was no known efficacy of imatinib freebase and imatinib mesylate, it is not possible to show that the beta crystalline form of imatinib has any enhanced efficacy.

The Court rejected both the arguments.

The Court clearly stated that the legislative intention shows very clearly that 'in course of the Parliamentary debates, the amendment in section 3(d) was the only provision cited by the Government to allay the fears of the Opposition members concerning the abuses to which a product patent in medicines may be vulnerable. We have, therefore, no doubt that the amendment/addition made in section 3(d) is meant especially to deal with chemical substances, and more particularly pharmaceutical products. The amended portion of section 3(d) clearly sets up a second tier of qualifying standards for chemical substances/pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds'.

On the second argument, the Court decided: 'On facts also we are unable to accept that imatinib mesylate or even imatinib was not a known substance with known efficacy. It is seen above that imatinib mesylate was a known substance from the Zimmermann patent. In the NDA [New

Drug Application] submitted by the appellant before the US FDA, it was clearly stated that the drug had undergone extensive preclinical, technical and clinical research.' Therefore the Court rejected the claim that the efficacy of imatinib mesylate or even imatinib was unknown.

Therefore on the question of the Section 3(d) test, the Court said 'it must be held that on the basis of the materials brought before this Court, the subject product, that is, the beta crystalline form of imatinib mesylate, fails the test of section 3(d), too, of the Act. We have held that the subject product, the beta crystalline form of imatinib mesylate, does not qualify the test of Section 3(d)'.

The Court also noted the fact that on the package the description of the drug includes 'each film coated tablet contains: 100 mg Imatinib (as Mesylate)' and there is no reference to the beta crystalline form of imatinib mesylate.

On the argument that there are two steps involved to develop the beta crystalline form of imatinib mesylate from the imatinib freebase, the Court remarked that 'this position is not reflected in the subject application, in which all the references are only to imatinib in free base form (or to the alpha crystalline form of imatinib mesylate in respect of flow properties, thermodynamic stability and lower hygroscopicity)'.

On the patent application on the beta crystalline form of imatnib mesylate, the Court observed: 'It may also be stated here that while going through the Zimmermann patent one cannot but feel that it relates to some very serious, important and valuable researches. The subject patent application, on the other hand, appears to be a loosely assembled, cut-and-paste job, drawing heavily upon the Zimmermann patent.'

Implications on the patenting of known substances

The most important outcome of the Court decision is its implication on the future of patenting of known substances. It is a well-known fact that multinational pharmaceutical corporations obtain multiple patents on the same molecule. Multiple patenting of known substances can delay the entry of generics and prevent competition in the pharmaceutical market.

The Court clearly recognised the policy concern with regard to patenting of known substances as reflected in Section 3(d) of the Indian Patents Act. Towards this end, it traced the legislative history of the Act, including the parliamentary debate over the 2005 amendment which introduced Section 3(d). The Court noted: 'In course of the debate in Parliament, an amendment (by way of addition) in clause (d) of section 3 was proposed by the Government in order to allay the fears of the members from the Opposition concerning the introduction of product patents for pharmaceuticals and agricultural chemicals, and it was on the Government's assurance that the proposed amendment in section 3(d) (besides some other changes in the Act) would take care of the apprehensions about the abuse of product patent in medicines and agricultural chemical substances that the Bill was passed by Parliament.'

Section 3(d) states that the following is not an invention within the meaning of the Patents 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. 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.'

One important critique of Section 3(d) is over the lack of explanation with regard to the word 'efficacy'. In the absence of a definition, the term 'efficacy' may lead to multiple interpretations. It can mean technological efficacy, therapeutic efficacy, economic efficacy or efficacy in the physical property of the substance.

The Court agreed with the Madras High Court's interpretation of the term and held that 'the explanation requires the derivative to "differ significantly in properties with regard to efficacy". What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly

relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy.'

Thus the Court clearly narrowed down the meaning of the term 'efficacy' to therapeutic efficacy. Further, the Court clearly stated that any improvement in the physical property does not pass the scrutiny of Section 3(d). The Court stated: 'While dealing with the explanation it must also be kept in mind that each of the different forms mentioned in the explanation have some properties inherent to that form, e.g., solubility to a salt and hygroscopicity to a polymorph. These forms, unless they differ significantly in property with regard to efficacy, are expressly excluded from the definition of "invention". Hence, the mere change of form with properties inherent to that form would not qualify as "enhancement of efficacy" of a known substance. In other words, the explanation is meant to indicate what is not to be considered as therapeutic efficacy.'

However, the Court did not examine what the requirements to prove enhancement in therapeutic efficacy are. It did not look into questions like whether increased bioavailability or less side-effect can be considered as an enhancement of therapeutic efficacy. These questions may be litigated in future. Hence, the decision on Novartis is a landmark decision but not the final decision.

Thus the Court further refined the application of Section 3(d) to curb the patenting of known substances. As mentioned above, the Court did not answer whether the beta crystalline form of imatinib mesylate satisfies the inventive-step criterion, i.e., whether the making of the beta crystalline form from the imatinib freebase or imatinib mesylate is obvious to a person skilled in the art. It made a passing reference that 'whether or not it involves an "inventive step" is another matter, and there is no need to go into that aspect of the matter now'. Such an examination by the Court could have resulted in much greater narrowing down of the patenting of known substances.

There is no doubt that the Novartis judgment is a landmark decision to further the resistance against abuse of patent monopolies in general and the efforts of developing countries to use the flexibilities in the TRIPS Agreement. The moot question is whether developing countries should replicate Section 3(d) in their patent legislation to check the patenting of known substances.

The main shortcoming of Section 3(d) is that it does not shut the door to patenting of known substances and it allows the patenting of known substances on a case-by-case basis if the patent applicant can prove that the claimed invention differs significantly in properties with regard to efficacy. In other words, Section 3(d) does not exclude the patenting of known substances per se and only limits it, requiring a case-by-case approach and examination of each patent application.

Hence, the replication of Section 3(d) as such is not suitable for developing-country settings facing a resource crunch. Further, Section 3(d) provides an element of discretion for the examiners and judges to interpret the term 'efficacy' and it may make these institutions vulnerable to lobbying. The scope of interpretation also may result in the undermining of the policy objective to curb the patenting of known substances by a narrow interpretation by the patent office or the judiciary.

Hence, it is always better for developing countries to provide for an ex ante exclusion of patenting of known substances without any substantive examination. Towards this end, what is required is a modified Section 3(d) which does not contain any scope for patenting of known substances in cases of enhancement of known efficacy.

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