

**WRITTEN SUBMISSIONS ON BEHALF OF THE INTERVENOR**

I    FACTS OF THE CASE ..... 3

    A    History of Glivec..... 3

    B    The Patents at Issue ..... 5

    C    Key Issues in the Dispute ..... 7

II   THE SECTION 3(D) STANDARD ..... 8

    A    Meaning of “Efficacy” ..... 9

        1    Drawing from the Orphan Drugs Act (ODA)..... 12

    B    Proving Efficacy..... 15

    C    When can proof of efficacy be submitted?..... 16

    D    Does Increased Bio-Availability Amount to Significantly Enhanced Efficacy?  
        17

    E    What is the “known substance” for the purpose of section 3(d)?..... 19

III   NOVELTY AND INVENTIVE STEP ..... 26

IV   PATENTS, PUBLIC ORDER AND EXCESSIVE PRICING ..... 28

IN THE SUPREME COURT OF INDIA

CIVIL APPELLATE JURISDICTION

I. A. NO. \_\_\_\_ OF 2011

IN

S.L.P. (C) NO. 20549/2009

**IN THE MATTER OF:**

NOVARTIS AG

...

PETITIONER

VERSUS

UNION OF INDIA & ORS.

...

RESPONDENTS

AND

**WRITTEN SUBMISSIONS ON BEHALF OF THE INTERVENOR****I      FACTS OF THE CASE****A      History of Glivec**

In 1960, Peter C Nowell, then a junior faculty member at the University of Pennsylvania School of Medicine, together with a graduate student, David Hungerford, discovered a genetic mutation in patients with chronic myelogenous leukemia (CML), a debilitating form of cancer. The discovery of this genetic abnormality designated the 'Philadelphia Chromosome' after the city in which it was discovered, broke fresh ground and spurred the search for a potential cure for CML. In the 1980's, researchers at the University of Chicago determined that the chromosomal abnormality produced a cancer-causing kinase enzyme.

With this enzyme as the target, Novartis researchers (led by Drs. Zimmermann and Buchdunger) in close collaboration with a prominent scientist, Dr. Brian Druker created and tested 400 molecules to find one that would inhibit this enzyme, without disrupting the hundreds of other similar enzymes in a healthy cell.

Pioneering the concept of rational drug discovery, they closed in on a promising candidate, "Imatinib," a free base. In 1993, Novartis filed a patent covering this free base and all pharmaceutically acceptable salts.

Imatinib was then further researched upon and improved by converting it to a particular salt form, namely imatinib mesylate. Novartis found that the most stable

version of this salt was a particular polymorphic form, namely the beta crystalline form. Novartis then formulated the beta crystalline form of imatinib mesylate into a pharmaceutically useful drug, Glivec [Known as Gleevec in US]. After its approval by the FDA in 2001, Glivec has proven effective for innumerable patients and has been hailed as nothing short of a wonder drug.

The various steps in the discovery and development of Glivec can be broken down as below:

1. Discovery of the Philadelphia Chromosome (a genetic mutation found in patients with Chronic Myeloid Leukemia): 1960
2. Discovery that the genetic abnormality results in a cancer causing kinase enzyme: 1980s (this enzyme is effectively the “target” that any drug must inhibit).
3. More than 400 compounds screened to assess for potential in inhibiting the enzyme (target): late 1980s
4. Scientists identify STI571 (Imatinib free base) as most promising “lead” that would inhibit the enzyme, without affecting other cells: 1992 <sup>1</sup>
5. Novartis files a patent claiming imatinib (free base) and all pharmaceutically acceptable salts: 1993<sup>2</sup>
6. Novartis files a patent claiming the beta crystalline version of imatinib mesylate, the active ingredient underlying the drug, Glivec: 1997

---

<sup>1</sup> See R Capdeville et al, *Glivec (STI571, Imatinib), A Rationally Developed, Targeted Anticancer Drug*, 1 *Nature Reviews Drug Discovery* 493-502 (2002) See Also E Buchdunger and J Zimmermann, The Story of Gleevec, <<http://www.innovation.org/index.cfm/StorieofInnovation/InnovatorStories/TheStoryofGleevec.html>> (last visited 31 August, 2011).

<sup>2</sup> U.S. Patent No. 5521184 (April 1993).

(Switzerland) and 1998 (India).<sup>3</sup> The Indian application claims priority from the Swiss application date: 18 July, 1997<sup>4</sup>

7. Glivec is granted FDA approval : 2001<sup>5</sup>

## **B The Patents at Issue**

The patent dispute that is now before this Hon'ble Court centres around the beta crystalline form of imatinib mesylate claimed in the 1998 patent application referred to above.

Novartis claims that about 40 patents covering this polymorphic beta crystalline form have been granted to it in various countries. However, owing to the unavailability of drug patents in India until 1 January 2005, Novartis claimed this new crystalline form in a "mailbox" application, which had been filed on 17 July, 1998.<sup>6</sup>

Pursuant to the 2005 amendment to India's patent regime, which introduced product patents for pharmaceuticals, the mailbox application by Novartis, as above mentioned, was opened and examined.

The grant of a patent was opposed by several generic drug companies (and an NGO,

---

<sup>3</sup> The patent was first filed in Switzerland in 1997 and then subsequently in the United States in 2000, claiming priority of the Swiss filing. See U.S. Patent No. 6894051 (January 2000).

<sup>4</sup> This finding of priority date was upheld by the Intellectual Property Appellate Board.

<sup>5</sup> Novartis Pharmaceuticals Corporation, *About Gleevec*, available at <<http://www.gleevec.com/patient/gleevec-prescription-medication-information.jsp>> (last visited 31 August, 2011).

<sup>6</sup> See Shamnad Basheer and Prashant Reddy, *The 'Efficacy' of Indian Patent Law: Ironing out the Creases in Section 3 (d)*, Scripted, Vol. 5, Issue 2 (August, 2008) also available at <[http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1086254](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1086254)> at 238 (last visited 12 August, 2011).

the Cancer Patients Aid Association (CPAA)) on several grounds including:

- i) lack of novelty/anticipation;
- ii) lack of significantly enhanced “efficacy” under section 3(d);
- iii) obviousness, and;
- iv) wrongful priority.

Agreeing with the above arguments, the Assistant Controller of Patents and Designs rejected the patent application.

Aggrieved by this rejection, Novartis AG, along with its Indian subsidiary, Novartis India, filed two writ petitions in the Madras High Court. These writ petitions not only sought a reversal of the Assistant Controller’s order, but also a declaration that section 3(d) was unconstitutional and in violation of India’s obligations under the TRIPS Agreement.

Pursuant to a Government notification, the Hon’ble High Court transferred the first writ petition to the Intellectual Property Appellate Board (IPAB) – a specialist tribunal set up to deal with appeals from the various intellectual property offices across the country. As for the second writ petition, it held that section 3(d) was constitutionally valid and that the TRIPS challenge was not maintainable; it could only be agitated before the WTO dispute settlement panel.

The IPAB effectively upheld the Controller's finding that the petitioners’ application was not patentable. In particular, it held that although the invention was novel and inventive, it could not be granted a patent since it (i) contravened section 3(d) and; (ii) violated public order under section 3(b).

**(i) Absence of significant enhancement of efficacy under section 3(d)**

The IPAB refused to accept that a 30% increase in bio-availability

demonstrated in favour of the beta crystalline form would lead to ‘significantly enhanced efficacy’ under section 3(d). Relying on the medical dictionary meaning of ‘efficacy’ as endorsed by the Madras High Court, the tribunal held that it is “the ability of a drug to produce a desired therapeutic effect”. The tribunal concluded that efficacy and bioavailability are not equivalent to each other. It further refused to read in ‘advantageous properties’ under the ambit of enhanced efficacy, reasoning that better storability, flow properties or shelf life, were concerned more with the formulation or presentability of a pharmaceutical substance, and had no relationship with the curing effect of the pharmaceutical substance. In the words of the IPAB,

*“Common sense tells that efficacy is a property which is related to curing effect of a drug, whereas better shelf life, better storability and better flow properties are something which is related to formulation or presentability of a drug/pharmaceutical substance which has no relationship with the curing effect. Hon’ble Madras High Court with the help of a dictionary on pharmacology has given a meaning of efficacy as therapeutic effect in healing a disease or having a good effect on the body.”(supra). We also are respectfully in full agreement with this meaning.”*

**(ii) Violation of Public Order due to excessive pricing of the claimed drug under section 3(b).**

The IPAB also held that the claimed invention was not eligible for a patent, under section 3(b), since the drug corresponding to the patent was marketed at an excessive and unaffordable price to patients in India. This, according to the IPAB, would be against ‘public order’ under section 3(b) of the Patent Act.

**C Key Issues in the Dispute**

The key issues now before this Hon’ble Court are:

1. Whether or not the petitioners' patent covering the beta crystalline version complies with section 3(d)?
2. Whether or not the said version is novel and inventive?
3. Whether or not it violates public order?

The intervenor seeks to assist the court with the above issues, and in particular to help it evolve guidelines for future pharmaceutical patent disputes. The interest of the intervenor lies in the robust development of sound patent jurisprudence for India that appropriately balances the competing interests of drug originators against that of generic companies and patients.

## II THE SECTION 3(D) STANDARD

Section 3(d) currently reads as under:

*“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 essence, section 3(d) stipulates that a new form of a known substance would be patentable only when the said new form demonstrates significantly enhanced

efficacy when compared with the known substance.<sup>7</sup> The key issues in interpreting the scope and ambit of section 3(d) are:

1. the meaning of the term efficacy
2. whether increased bioavailability qualifies as efficacy?
3. the standard of proof required to establish efficacy
4. the point in time at which proof of efficacy must be adduced
5. what is the known substance under section 3(d)?

#### **A Meaning of “Efficacy”**

The central issue in section 3(d) revolves around the meaning of the term “efficacy”. More specifically, the issue is whether or not efficacy ought to be interpreted narrowly to mean only “therapeutic” efficacy or whether it ought to be broadened out to include any kind of advantageous property attributable to the new form in question.

The Madras High Court held that “efficacy” meant only “therapeutic” efficacy and not every advantageous property claimed for the new drug derivative in question.<sup>8</sup> The IPAB endorsed this interpretation.

The intervenor submits that, based on the history of the section 3(d) and its current structure, this appears to be a correct reading of section 3(d). However, one important caveat needs to be borne in mind; section 3(d) is not limited to pharmaceutical technology alone. Rather, it applies also to chemicals (such as paints) and agro-chemicals (such as pesticides), for which therapeutic efficacy

---

<sup>7</sup> Section 3(d) of the Indian Patents Act, 1970. For an elaborate discussion of this provision, See Basheer and Reddy, *Supra* note 6.

<sup>8</sup> *Novartis AG & Anr. v. Union of India & Othrs.*, (2007) 4 MLJ 1153 at para 13 also available at <<http://www.indiankanoon.org/doc/1111498/>> (last visited 12 August, 2011).

cannot be an appropriate standard.<sup>9</sup>

A nuanced interpretation of efficacy would therefore suggest that it be defined in a technologically specific way i.e. while it would mean therapeutic efficacy in the pharmaceutical context, it would translate to an ability to destroy pests in a pesticide context. Such an interpretation is in conformity with prevailing patent jurisprudence in countries such as the US and EU which have been known to interpret facially neutral patent standards in a technologically specific way.<sup>10</sup>

The structure of section 3(d) as also its legislative history supports a narrow reading of the term “efficacy”.

Illustratively, the Explanation to section 3(d) clearly states that all pharmaceutical derivatives would be considered the same “substance”, unless “*they differ significantly in properties with regard to efficacy.*”

The above clause refers to only those “properties” that have some bearing on “efficacy” and not all properties. Therefore, not all advantageous properties of a new form ought to qualify under section 3(d), but only those properties that have some bearing on efficacy. Although this precise line of argument pointing to the phrase “properties with regard to efficacy” does not appear to have been explicitly made by either the Madras High Court or the IPAB to support their conclusion, it is one that compellingly supports a restrictive interpretation of the term “efficacy”.

---

<sup>9</sup> *Supra* note 6 at 244.

<sup>10</sup> See Dan L Burk and Mark A Lemley, *Policy Levers in Patent Law* 89 Va. L Rev. 1575, 1662 (2003). See Also Dan L Burk and Mark A Lemley, *Is Patent Law Technology-Specific?* 17 Berkeley Tech. L.J. 1155, 1184 (2002).

This interpretation is further buttressed by the objectives of the Act, which suggest that section 3(d) was introduced to prevent ever-greening.<sup>11</sup> The Madras High Court states in this regard:<sup>12</sup>

*“...We have borne in mind the object which the Amending Act wanted to achieve namely, to prevent ever-greening; to provide easy access to the citizens of this country to life saving drugs and to discharge their Constitutional obligation of providing good health care to it's citizens...”*

Although the term ever-greening does not have a scientific definition as yet, it is widely understood to mean an inappropriate extension in patent monopoly which does not convert to a significant benefit for the patient.<sup>13</sup>

Put another way, it is a patenting strategy “consisting of acquiring patents on minor, often trivial, modifications of existing pharmaceutical products or processes in order to indirectly extend the period of patent protection over previously patented compounds.”<sup>14</sup>

---

<sup>11</sup> See Transcript of Parliamentary Debate, March 22, 2005, where Shri Kurup makes a statement indicating that the section is being brought in to prevent ever-greening. See also statements of Madras High Court in this regard.

<sup>12</sup> *Supra* note 8, para 19.

<sup>13</sup> 'Ever-greening' is not a formal concept of patent law. It is best understood as a social idea used to refer to the myriad ways in which pharmaceutical patent owners utilise the law and related regulatory processes to extend their high rent-earning intellectual monopoly privileges, particularly over highly profitable (either in total sales volume or price per unit) 'blockbuster' drugs. T. A. Faunce & J. Lexchin, *'Linkage' pharmaceutical ever-greening in Canada and Australia*, available at: <<http://law.anu.edu.au/StaffUploads/236-Art%20ANZHP%20Linkage%20Evergreening.pdf>> (last visited 31 August, 2011).

<sup>14</sup> See Carlos Correa “Guidelines for Examination of Pharmaceutical Patents”, available at: <[http://www.iprsonline.org/resources/docs/Correa\\_Patentability%20Guidelines.pdf](http://www.iprsonline.org/resources/docs/Correa_Patentability%20Guidelines.pdf)> (last visited 31 August, 2011). See Also A. Kesselheim, *Intellectual Property Policy in the Pharmaceutical Sciences: The Effect of Inappropriate Patents and Market Exclusivity Extensions on the Health Care System*, available at: <<http://www.aapsj.org/view.asp?art=aapsj0903033>> (last visited 31 August, 2011) “patent ever-greening,” is the patenting of nonessential features of products, including aspects of their formulation, their metabolites, or methods of administration.”).

## 1 Drawing from the Orphan Drugs Act (ODA)

Based on all of the above, the intervenor submits that the term efficacy under section 3(d) ought to be interpreted to mean any “therapeutic advantage”. The Orphan Drugs Act is illustrative in this regard and could be used to delineate the contours of “therapeutic advantage”.

The ODA was enacted by the US Congress to help incentivise the creation of what are known as “orphan drugs” i.e. any drug used to treat a rare disease or condition that affects fewer than 200,000 patients in the US or for which there is no reasonable expectation that the cost of developing the drug for a disease will be recovered from sales.<sup>15</sup>

Given that pharmaceutical companies generally shy away from research on orphan drugs, owing to the lack of large markets for such drugs, the ODA was brought into existence to grant additional incentives for creating such drugs to benefit minority patient populations. The incentive is in the form of a seven year marketing exclusivity to drug originators, so that they are able to recover their R&D costs and also make a healthy profit during this period of exclusive protection.<sup>16</sup> Contrast this with regular data exclusivity regimes, which grant drug originators a period of exclusivity lasting only 5 years from the date of their approval. Further, such exclusivity is limited to preventing the use of and reliance upon “data” submitted by the drug originator to regulatory authorities, such that no follow-on drug manufacturer’s drug can be approved using this very same data during the time of protection. However, follow-on manufacturers are free to conduct their own clinical trials and procure drug marketing approval during this time period.<sup>17</sup>

---

<sup>15</sup> 21 USC §360ee(b) (2) (1994).

<sup>16</sup> *Infra* note 17 at 371.

<sup>17</sup> Robert A. Bohrer and John T. Prince, *A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 Harv. J. L. & Tech. 365, 370 (1999).

Contrast this with the ODA which offers complete and absolute “market” exclusivity, independent of the clinical trial data that is submitted. In other words, the protection is against all follow-on drug manufacturers, who cannot enter the market, even if they repeat the clinical trials and are able to submit independently generated data.<sup>18</sup>

Complete market exclusivity, as opposed to mere data exclusivity, would mean that no follow-on manufacturer can make or sell a version containing the same active ingredient or claiming the same “indication” or “use”, even if they are able to generate their own data for the same. However, the issue of “sameness” has been a highly contentious one under the ODA.

The FDA regulations on this count suggest that “clinical superiority” would render a structurally similar drug molecule “different” from the original drug entitled to orphan drug exclusivity.<sup>19</sup>

The regulations define a "clinically superior" drug as one that "is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug . . . ."

Therapeutic advantage, or clinical superiority<sup>20</sup>, can be shown in one of three ways: (1) greater effectiveness; (2) greater safety; or, (3) demonstration that the drug

---

<sup>18</sup> Unlike other types of exclusivities for new drugs, the law provides complete market exclusivity for orphan drugs for a seven-year period, thereby preventing a competitor from entering the market, even if it were able to generate its own data. *See* Orphan Drug Act, 1983.

<sup>19</sup> "With regard to macromolecular drugs, clinical superiority by itself will render a subsequent drug different." *See* Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,081 (1992) at 62,078. This "clinical differences" standard was based on the principle that the market exclusivity should not create a barrier to needed patient therapies. *See* Joseph A Levitt & John V Kelsey, *The Orphan Drug Regulations and Related Issues* 48 Food & Drug L.J. at 528-29.

<sup>20</sup> The terms therapeutic advantage and clinical superiority are interchangeable. Therapeutic advantage is demonstrated when clinical testing of a drug demonstrates it to be superior in an important dimension. *See* 21 C.F.R. §. 316.3 (b) (3) (iii) (1999).

makes a major contribution to patient care in "unusual cases."

To demonstrate greater effectiveness, the same kind of evidence is needed as that generally required to support a comparative effectiveness claim for two different drugs; that is, an improvement as assessed by the drug's "effect on a clinically meaningful endpoint in adequate and well controlled clinical trials."<sup>21</sup>

To support a claim of superior safety, the company seeking approval of the second product must establish that its product provides "greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects."<sup>22</sup>

Finally, a second drug can be considered "clinically superior" if it makes some other "major contribution to patient care." The FDA intends this to be "a narrow category," such as, for example, "the development of an oral dosage form where . . . only a parenteral dosage form" had existed previously.<sup>23</sup>

It bears noting that the ODA norms above mentioned are not strictly "regulatory" in nature. Rather, they act as incentives for innovation in a manner similar to patents. Therefore these norms seem appropriate for providing guidance in a patentability context, such as in interpreting efficacy under section 3(d).

However, a key limitation must be noted in this regard: In order to evaluate "sameness" under the ODA, one is always likely to have two drugs i.e. the drug which is protected for 7 years under the ODA and the new drug which is allegedly similar to the old protected drug.

---

<sup>21</sup> *Supra* note 17 at 392-393.

<sup>22</sup> *Supra* note 17, 393.

<sup>23</sup> *See* 21 C.F.R. §. 316.3 (b) (3) (iii) (1999).

In a section 3(d) context however, the old substance against which the therapeutic advantage comparison is made, may not be a drug (as is the case with imatinib or even imatinib mesylate in a form other than the beta crystalline version). Further, in some cases where patent applications are filed to claim new forms, such a new form may not be a fully developed drug at the time that the patent application is filed. In fact, in most cases, it is likely that the point of time at which a new form is claimed as a patent is prior in time to its being developed as a drug and submitted to the drug regulator for regulatory approval.

It is therefore submitted that the standard of proof required to demonstrate significant therapeutic advantage cannot be as onerous as that expected for drug regulatory regimes such as the ODA, an aspect dealt with in the section below.

## **B Proving Efficacy**

It is submitted that section 3(d) ought not to be interpreted in the same way as a regulatory standard, when it comes to evidentiary requirements.

The drug innovation process could be broadly divided into two phases, namely “drug discovery” and “drug development”. Patents are typically filed at the upstream drug discovery stage, when all that the applicant has is a potentially viable drug molecule. It is only later that the drug is developed and tested through a series of clinical trials and finally brought into the market after procuring regulatory approval. The time gap between discovering a drug molecule and developing it into a marketable drug can take several years.

Therefore, in many cases, it is unlikely that at the patenting (drug discovery) stage, the applicant would possess any clinical trial data at all. It would be irrational and even unethical to insist on clinical trial evidence only for the purpose of satisfying

patentability requirements under section 3(d).<sup>24</sup> It is therefore submitted that the standard of proof be as under:

*The applicant need not prove “efficacy” under section 3(d) as a matter of statistical certainty. Nor does the applicant have to provide actual evidence of trials in humans. Instead, the applicant has to demonstrate a reasonable correlation between the efficacy claimed and the data provided in support of this. Such reasonable evidence of the correlation can be established by relying on, inter alia, statistically relevant data documenting the activity of the new form and/or known substance, documentary evidence (e.g. articles in scientific journals), data generated using in vitro assays, or from testing in an animal model, other preclinical test data or any combination thereof.*<sup>25</sup>

It could be argued that insisting on clinical trial type proof under section 3(d) would contravene the Helsinki Declaration, principle 21 of which states that trials and other experiments on humans can be performed only if the importance of the objective outweighs the inherent risks and burdens to the research subjects. Subjecting human subjects to clinical trials for the sole purpose of crossing the threshold of section 3 (d) is unethical and unwarranted.

It bears reiteration that section 3(d) not only calls for a comparison with druggable substances, but even with substances that may never be suited for conversion to drugs, so long as the said substance qualifies as a “known substance” under section 3(d). Administering such non-druggable forms to human volunteers only with a view to crossing the section 3(d) threshold is highly unethical.

### **C When can proof of efficacy be submitted?**

---

<sup>24</sup> *Supra* note 6 at 255-256.

<sup>25</sup> *Supra* note 6, at 256.

In so far as pharmaceutical patent applications were filed prior to the introduction of the 2005 Patent Amendments, the patent office must permit the patent applicant an opportunity to file documentation/evidence in support of section 3(d) at the time that it reviews the application for the first time. This is only fair and just, as the patent applicant could not have known of the future existence of section 3(d) at the time of filing her patent application. However, in so far applications filed after the coming into force of the Patents (Amendment) Act, 2005 are concerned, no such opportunity need be provided. In such cases, if the filed specification does not contain any evidence of increased efficacy, the patent office is entitled to reject the application.

**D Does increased bioavailability amount to significantly enhanced efficacy?**

It is humbly submitted that the short answer to this is this: it depends. As noted earlier, efficacy ought to be interpreted to mean a definite “therapeutic advantage”. As to whether or not a showing of increased bioavailability also converts to an added therapeutic advantage has to be assessed on a case-by-case basis; the answer cannot be a blanket yes or no.

Bioavailability means “the rate and extent to which the active drug ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action”<sup>26</sup>

It is usually determined by measuring the concentration of a substance in biological fluids as a function of time, or by excretion of a substance as a function of time, or by acute pharmacology effect.<sup>27</sup>

---

<sup>26</sup> See 21 CFR Section 320.1(a).

<sup>27</sup> See 21CFR Sec 320.24.

In some cases, a new form with increased bio-availability might confer significant benefits in terms of reduced toxicity. Assume that the earlier known substance had to be administered at 10gm to be therapeutically effective, but that this 10 gm was significantly toxic to the patient. If the new form now enables 5 gm to deliver the same therapeutic impact with greatly reduced or no toxicity at all, this is a significant clinical advantage in so far as the patient is concerned. Such enhanced patient advantage ought to count as “efficacy” under section 3(d).<sup>28</sup> It is pertinent to note in this regard that the regulations in relation to the ODA state that a “diminution in adverse reactions may be sufficient to allow a finding of clinical superiority.”<sup>29</sup>

In other cases, it is possible that an increase in bio-availability does not convert to any significant therapeutic advantage at all.

In the specific facts of the case under dispute before this Hon’ble Court, the Petitioner sought to establish that when compared with the Imatinib free base, the beta crystalline form demonstrates a 30% increase in bio-availability. However, this by itself does not demonstrate any therapeutic advantage in relation to the patient. Such advantage has to be independently established.

It is humbly submitted that “it is not the intent of a bio-availability study to demonstrate effectiveness, but to determine the rate and extent of absorption. If a drug product is not bio-available, it cannot be regarded as effective. However a determination that a drug product is bio-available is not in itself a determination of effectiveness.”<sup>30</sup>

---

<sup>28</sup> *Supra* note 6 at 243-244.

<sup>29</sup> Orphan Drug Regulations, 57 Fed. Reg. 62,078, *See supra* sub part Orphan Drug Act at 8-9.

<sup>30</sup> 42 FR 1640 (1977). Cf. Moffitt, Jane, *Appropriateness of Bioavailability and Bioequivalency as Pre-Market Clearance Considerations*, 34 Food Drug Cosm. L.J. 640 (1979).

**E      What is the known substance for the purpose of section 3(d)?**

For an appropriate determination under section 3(d), the primary issue is: what is the “known substance” against which the enhanced “efficacy” comparison ought to be made?

Would the “known” substance be the imatinib free base (in relation to which it is far easier to show increased efficacy) or the later salt, imatinib mesylate? Or a polymorphic form of the salt, such as the alpha crystalline form? Or a combination of one or more of the above?

The section 3(d) evidence submitted by the Petitioner to the Patent Office compares only the Imatinib free base (as disclosed in the 1993 patent) with the beta crystalline version. It demonstrates a higher bio-availability for the beta crystalline form when compared with the free base. In other words, it treats only the imatinib free base as the “known substance” that is closest in structure to the claimed beta crystalline form. However, this may not necessarily be correct. Rather the identification of the “known substance” would hinge upon the issue below:

Could a person skilled in the art have produced imatinib mesylate from the teaching of the 1993 patent and other prior art existing up to 18 July, 1997 (the priority date of the patent application covering the beta crystalline form) without undue experimentation? And if yes, in what form would such imatinib mesylate be obtained?

Assuming imatinib mesylate in form X could have been obtained from the teachings of the prior art existing as on 18 July, 1997 then “imatinib mesylate in Form X” is the “known” substance for the purpose of comparison.

The key test in this regard is: “could a skilled person arrive at this substance (Imatinib Mesylate in Form X) without undue experimentation”?<sup>31</sup>

It is humbly submitted that the standard for determining “known” substance under section 3(d) ought to be the same as that used for determining novelty and anticipation under traditional patent law i.e. whether substance X that is claimed in a patent application is already part of the prior art and therefore anticipated? The test thus far employed in US and EU suggests that X is anticipated only if the prior art teaches a person skilled in the art to reproduce X without undue experimentation.

In this regard, the intervenor wishes to draw the attention of the court to a British case, *Synthon BV v. SmithKline Beecham*.<sup>32</sup> In *Synthon*, the appellant *Synthon BV* applied to revoke *Smith Kline’s* patent for a particular crystalline form of the blockbuster drug paroxetine, based on *Synthon's* own earlier patent application. Although *Synthon* was successful at the first instance, the court of appeals reversed the decision. *Synthon* accordingly appealed to the House of Lords.

The leading opinion of the House of Lords was given by Lord Hoffman, who held that anticipation required proof of two distinct matters (1) the invention had been disclosed (2) the invention had been enabled viz. an ordinary skilled man would have been able to perform the disclosed invention if he attempted to do so by using the disclosed matter and common general knowledge.

---

<sup>31</sup> *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education & Research* 346 F. 3d 1051 (Fed. Cir. 2003) where it was held that “invalidity based on anticipation requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus of the patented invention without undue experimentation.” In *Schering Corporation v. Geneva Pharmaceuticals Inc.* 339 F.3d 1373 (Fed. Cir. 2003) the court held that a prior art reference may anticipate through inherency the entirety of a later claimed compound even though that compound was never mentioned in the prior art.

<sup>32</sup> *Synthon BV v. SmithKline Beecham plc* [2006] RPC 10.

Lord Hoffman set out in some detail the law relating to “disclosure” and “enablement”, while emphasising the importance of keeping these two concepts distinct.

On the issue of “disclosure”, Lord Hoffmann began by quoting Lord Westbury in *Hill v Evans*<sup>33</sup>:

*“...the antecedent statement must be such as a person of ordinary knowledge of the subject would at once perceive, understand and be able practically to apply the discovery without the necessity of making further experiments and gaining further information before the information can be made useful...”*

On the issue of “enablement”, Lord Hoffmann observed that enablement means ‘that the ordinary skilled person would have been able to perform the invention which satisfies the requirement of disclosure’. Enablement in the context of novelty, according to Lord Hoffman was the same as enablement for the purpose of determining sufficiency. However, while determining sufficiency the skilled person has the goal of the invention clearly in mind. While assessing enablement for novelty, prior art cannot be assessed with the benefit of hindsight and knowledge of the claimed invention. He thereafter quoted L. J Buckley in *Valensi v. British Radio Corp*<sup>34</sup> on what will satisfy the requirements of enablement for the purpose of sufficiency

*“...the hypothetical addressee is not a person of exceptional skill and knowledge, which he is not to be expected to exercise any invention nor any prolonged research, inquiry or experiment. He must, however, be prepared to display a reasonable degree of skill and common knowledge of the art in making trials and to correct obvious errors in the specification if a means of correcting them can readily be found...”*

---

<sup>33</sup> *Hill v. Evans* (1862) 31 L.J. N.S. 457.

<sup>34</sup> *Valensi v. British Radio Corporation* [1973] R.P.C 337.

It is important to note that disclosure and anticipation are distinct requirements, and proof needs to be submitted on both. In assessing disclosure, no aspect of trial or error is permitted. In assessing whether or not the disclosure is enabled, a reasonable degree of experimentation can be expected and is permissible. Depending on the concept under consideration, the role of the skilled person is different. In assessing disclosure, the skilled person is attempting to discern what the author of the prior document art meant.

In assessing enablement, the skilled person is not concerned with what the prior art may have meant, but rather, whether the invention disclosed by the prior art could be made to work. As such, disclosure is an inquiry as to construction. Enablement is an inquiry as to what the skilled man would or would not be able to achieve. The importance of the separation of these two concepts is evident particularly in cases of simple “low-tech” inventions, where a simple disclosure of an invention will probably be enough to enable it, but in cases of high-tech inventions, the basic assertion of the existence of an invention may disclose it, but it may well require additional detailed description to enable a skilled person to perform it.<sup>35</sup>

Unfortunately, the decisions of the lower fora (the patent office and the IPAB) do not reflect a thorough assessment of the “enablement” or “disclosure” standard and its application to the facts in this case.

It is submitted that merely because the 1993 Patent claims or mentions the imatinib mesylate salt does not automatically mean that the salt is enabled. In fact, if it is found by a court that the salt is not enabled by the 1993 patent, the court is entitled to strike down that claim as invalid. However, it bears noting that the validity of the 1993 patent, a registered US patent is not at issue before this Hon’ble Court.

---

<sup>35</sup> See A Sharples and D Curley, *‘Experimental Novelty: Synthron v. SmithKline Beecham’*, 28(5) E.I.P.R 308-311 (2006); See Also A. Batteson, *Patents: Enabling Disclosures* 28(2) E.I.P.R 28 (2006).

The same logic holds true also for any disclosure of imatinib mesylate in the 1996 prior art articles. In the own words of the IPAB

*We have also 'Cancer Research' article of Jan. 01, 1996 (56, 100-104) relied upon by the Respondents which actually used the substance imatinib mesylate for tests. The Appellant's specification also refers to the use of this salt stated to be reported in "Nature Med." 2, 561 -6 (1996). Thus, there is no doubt that such a substance was in existence or in use in 1996 before the priority date of the impugned application...'*

The IPAB fails to see the distinction between the alleged disclosure of a substance and an enabling disclosure. It must be borne in mind that the imatinib mesylate salt, mentioned in the 1996 'Cancer Research' Article<sup>36</sup> was known only to Ciba Corporation and its scientists (the predecessor of Novartis). Therefore, the mere fact that imatinib mesylate finds mention in this article written by insiders cannot be taken to mean that it is indeed now known to the public. Even assuming the skilled person could have arrived at imatinib mesylate from the teachings of the prior art, the decision of the IPAB does not indicate as to what form such imatinib mesylate would be obtained in.

It appears to hint that this could be the "amorphous" version of Imatinib mesylate but does not offer any basis for how it arrived at this conclusion. In the words of the IPAB

*"...Though no working example for preparing a salt has been given in the said 1993 patent we are of the opinion that it is not impossible for a person skilled in the art to prepare imatinib mesylate from imatinib by a conventional process as suggested in the said 1993 patent. But as no possibility of polymorphism, which is not a general phenomenon of a salt, can be predicted from that salt from any prior document, it is*

---

<sup>36</sup> E. Buchdunger et al., Inhibition of the Abl- Protein-Tyrosine Kinase in Vitro and In Vivo by a 2-Phenylaminopyrimidine Derivative, (1996) 56 *Cancer Res.* 100-104, available at <<http://cancerres.aacrjournals.org/content/56/1/100.long>> (last visited on 31 August, 2011).

*not possible for an un inventive man to discover the same and reach to the beta crystal form of imatinib mesylate, or to find its advantageous properties or to find a suitable process for its preparation or make a solid pharmaceutical composition containing the said crystal form...”*

The above paragraph does not really inform us as to how the skilled person could have produced an amorphous version of Imatinib Mesylate, using only prior art knowledge and techniques existing up to July 1997, the priority date of the patent application. It is submitted that such a conclusion could be arrived only on the basis of expert evidence testifying as to what the skilled person was capable of doing as on the priority date.

It bears noting in this regard that there was evidence on record (the IIT/IICT reports) demonstrating that the natural form of expression of imatinib mesylate would be the beta crystalline form. In other words, the IIT/IICT reports which were filed by the petitioner’s opponents suggested that the prior art knowledge could be used to produce the beta crystalline version of imatinib mesylate directly.

The IPAB however disagrees with this evidence, without offering any credible reasons for disagreement. Here again, such an assessment can be arrived only on the basis of expert evidence testifying as to what the skilled person was capable of doing as on the priority date. Such assessment on the basis of such expert testimony is not reflected in the IPAB’s decision.

In short, it is not clear whether or not a skilled person could obtain imatinib mesylate from the teachings of the prior art? And if so, in what form? Would it be obtained in the beta crystalline, alpha crystalline or the amorphous form? Or a combination of all three?

It is therefore humbly requested that the court appoint an independent expert to make this determination. In accordance with section 115 of the Patent Act, the court is conferred with the powers to appoint an independent scientific adviser to assist them or to inquire and report on any question of fact or opinion, not involving a question of interpretation of law. It provides

*“115. Scientific Advisers: (1) In any suit for infringement or in any proceedings before a court under this Act, the court may at any time, and whether or not an application has been made by any party for that purpose, appoint an independent scientific adviser to assist the Court or to inquire and report upon any such question of fact or of opinion (not involving a question of interpretation of law) as it may formulate for the purpose.*

*(2) The remuneration of the scientific adviser shall be fixed by the court and shall include the costs of making a report and a proper daily fee for any day on which the scientific adviser may be required to attend before the court, and such remuneration shall be defrayed out of moneys provided by Parliament by law for the purpose.”*

The appointment of such scientific advisers can be made by the court *suo moto* or on an application by the parties. Considering that patent proceedings often involve complicated scientific and technical issues, the assistance of such advisers, may be indispensable in determining issues before the court. It may be noted, that the aforesaid provision, is in addition to the powers of the court to admit ‘expert evidence’ as defined under section 45 of the Evidence Act, 1872.

Therefore, it is prayed that this Hon’ble Court may appoint an independent scientific adviser to determine whether or not a skilled person could obtain imatinib mesylate from the teachings of the prior art, and if so, in what form would he/she obtain it. Such an expert should ideally be a renowned academic or independent researcher

with expertise in pharmacology and with no direct interest in this dispute under consideration.

### III NOVELTY AND INVENTIVE STEP

The key issues are:

1. Was the beta crystalline version of imatinib mesylate effectively enabled by the 1993 patent and subsequent literature that preceded the priority date of the 1998 patent application covering the beta crystalline version (as noted earlier, the priority date for the 1998 application is 18 July, 1997)
2. Even if it was not enabled by the prior art, could the beta crystalline form have been said to be obvious to a skilled person from the prior art?

If the person skilled in the art attempting to produce imatinib mesylate (as per the disclosure in 1993 patent and other relevant prior art existing up to July 1997) would necessarily produce the beta crystalline version (since the compound naturally expresses itself in this form), then the beta crystal will be found to have been anticipated. Such a conclusion holds good even if such a skilled person obtaining the beta crystalline form is unable to characterize it as a beta crystalline form.

It is submitted that in such cases, the beta crystalline form is anticipated under the doctrine of inherent anticipation, a doctrine explicated well in *Schering Corp. v. Geneva Pharmaceuticals, Inc.*<sup>37</sup>

---

<sup>37</sup> 339 F.3d 1373, 1382 (Fed.Cir. 2003).

In this case, Schering had a patent covering loratadine, an antihistamine marketed as Claratin. Schering subsequently filed a second patent on descarboethoxyloratadine (“DCL”) that is naturally produced by the human body as a metabolite of loratadine.<sup>38</sup> Notwithstanding the lack of any prior art teaching of DCL, or any other metabolite of loratadine, the Court held that Schering’s prior art patent claiming loratadine inherently anticipated its subsequent patent. This is because DCL was “necessarily and inevitably” formed upon the metabolism of loratadine.

Inherent anticipation does not require that the inherent feature be appreciated or recognized at the time of the earlier patent, as long as the disclosure is a "necessary and inevitable" consequence of the earlier invention.<sup>39</sup>

Based on the above, if the beta crystalline version automatically results from the teachings of the prior art, it is anticipated, even if the skilled person is unable to identify or characterize it.

Conversely, if the beta crystalline version does not automatically result from the teachings of the prior art, it cannot be held to be anticipated. However, it may still be held to be obvious to a person skilled in the art, in the light of prior art.

The IPAB concludes that the beta crystalline form of imatinib mesylate is not obvious and involves an inventive effort on the part of Novartis. In the words of the IPAB

---

<sup>38</sup> *Id.* at 1375.

<sup>39</sup> *Supra* note 37 at 1378-80

*“...We observe that no concrete method has been disclosed in the prior art to prepare even imatinib mesylate. Since, it can exist in several other polymorphic forms also as has been argued by the Appellant and not disputed by the Respondents that no one can say with certainty that one would reach directly to beta by a generally conventionally known prior art procedure. IICT and IIT experiments getting only beta do not prove that any process for converting imatinib to imatinib mesylate will inevitably lead to the beta form [see paragraph 9 (xi) supra]. If that be the case then how several other forms of it could be prepared from imatinib which are still in existence? It would be an inventive effort to find out the exact process conditions to get to a particular form including that of the beta form. It is not always correct that only the stable form would only result out of a chemical reaction or a stable form can not be converted into a relatively unstable one. We also do not have any evidence on record which suggests that a given form of imatinib mesylate automatically converts itself to only the beta form on storage...”*

The above conclusion appears conclusory, as it is not based on any expert evidence testifying as to what the skilled person might have done or been capable of doing based on prior art knowledge existing at that time. The intervenor therefore requests that this Hon'ble Court appoint an independent expert to determine whether or not the prior art would have rendered the production of Imatinib Mesylate in a beta crystalline form obvious?

#### **IV PATENTS, PUBLIC ORDER AND EXCESSIVE PRICING**

The IPAB held that the beta crystalline form of imatinib mesylate was not eligible for a patent under section 3(b), since a drug corresponding to the patent had been priced excessively. Section 3(b) currently reads as under:

*“3. What are not inventions: The following are not inventions within the meaning of*

*this Act....*

*(b) an invention the primary or intended use or commercial exploitation of which could be contrary to public order or morality or which causes serious prejudice to human, animal, plant life or health or to the environment*

According to the IPAB, the excessive price of Glivec would wreck havoc in the lives of poor cancer patients and their families, creating public disorder and was therefore ineligible for a patent. In the words of the IPAB

*“...But as per information furnished in its written counter-argument by R 3 that when the Appellant was holding the right as EMR on GLEEVEC it used to charge Rs. 1, 20,000/- per month for a required dose of the drug from a cancer patient, not disputed by the Appellant, which in our view is too unaffordable to the poor cancer patients in India. Thus, we also observe that a grant of product patent on this application can create a havoc to the lives of poor people and their families affected with the cancer for which this drug is effective. This will have disastrous effect on the society as well. Considering all the circumstances of the appeals before us, we observe that the Appellant’s alleged invention won’t be worthy of a reward of any product patent on the basis of its impugned application for not only for not satisfying the requirement of section 3(d) of the Act, but also for its possible disastrous consequences on such grant as stated above, which also is being attracted by the provisions of section 3(b) of the Act which prohibits grant of patent on inventions, exploitation of which could create public disorder among other things...”*

It is submitted that this is a ludicrous legal proposition. Under current Indian patent law, the excessive price of a drug cannot be a ground for denying a patent to an invention underlying the said drug. The key issue at the time of granting a patent is whether the invention represents a good enough technical/scientific advance to merit a twenty year monopoly?

Any potential for patent abuse is redressable through a number of *ex-post* (prospective) mechanisms such as compulsory licensing and price control and ought not to factor in during the stage of grant of a patent. not least because very often, there is no product at the stage of grant of a patent.

Secondly, such an additional patentability criterion could fall foul of TRIPS. Under Article 27 of TRIPS, all inventions (barring those mentioned in paragraphs 2 and 3 of that Article) are patentable. Although the terms *ordre public* or morality are fairly subjective and dependent on the particular socio-cultural mores of a country at a given point in time,<sup>40</sup> an exception based on ‘public ordre’ and ‘morality’ in Article 27.2 can be applied only when it is *necessary* to prevent the “commercial exploitation” of the invention.<sup>41</sup> In other words, Article 27.2 of the TRIPS applies only if a prohibition against the commercial exploitation of the invention is necessary to protect *ordre public* or morality and only if the exclusion from patentability will likewise contribute to the protection of that *ordre public* or morality.<sup>42</sup> This could suggest, as some have argued, that in order to justify a patent as immoral or against public order, one must first have a law which prevents the commercial exploitation of the particular product.<sup>43</sup> Or one must at least show the

---

<sup>40</sup> Basheer, Purohit and Reddy, “Patent Exclusions that Promote Public Health Objectives” Report by Bentley et al “Exclusions from Patentability and Exceptions and Limitations to Patentees’ Rights”, WIPO Standing Committee on the Law of Patents, SCP/15/3, September 2010, available at <[http://www.wipo.int/edocs/mdocs/scp/en/scp\\_15/scp\\_15\\_3-annex1.pdf](http://www.wipo.int/edocs/mdocs/scp/en/scp_15/scp_15_3-annex1.pdf)>.

<sup>41</sup> Patents: *Ordre Public and Morality*, Resource Book on TRIPS and Development, available at <[http://www.iprsonline.org/unctadictsd/docs/RB2.5\\_Patents\\_2.5.3\\_update.pdf](http://www.iprsonline.org/unctadictsd/docs/RB2.5_Patents_2.5.3_update.pdf)> (last visited 31 August, 2011).

<sup>42</sup> Charles R. McManis, *Patenting Genetic Products and Processes: A TRIPS Perspective*, available at <[http://law.wustl.edu/faculty\\_profiles/documents/Kieff/HGPIP/Final/GEN\\_50\\_CH5.pdf](http://law.wustl.edu/faculty_profiles/documents/Kieff/HGPIP/Final/GEN_50_CH5.pdf)> (citing Nuno Pires de Carvalho, *The TRIPS Regime of Patent Rights* 170-173 (2003)) (last visited 31 August, 2011).

<sup>43</sup> Nuno Pires De Carvalho, *The TRIPS Regime of Patent Rights*, 2<sup>nd</sup> edn. Kluwer Law International, Hague 2005 at 209.

existence of circumstances necessitating such a law or ban.<sup>44</sup> Under such an interpretation, unless India bans the sale of Glivec or shows that Glivec is otherwise harmful, it cannot exclude a patent covering it on the grounds of public order or morality.

Secondly, Article 27.2 appears to be predicated on a “necessity test” to assess whether protection of an overriding social interest is justified.<sup>45</sup> Therefore, any measure taken is justified only if no reasonable alternative is available to a Member. Here, as stated above, alternatives such as compulsory licensing, price control mechanisms are ‘reasonably available’. Hence in this case, one might argue that the conditions of Article 27.2 of TRIPS have not been satisfied.

For all the above reasons, it is submitted that the rejection of a patent based on excessive price of the final patent product has no basis in Indian patent law.

---

<sup>44</sup> See Dan Leskien & Michael Flitner, ‘Intellectual Property Rights and Plant Genetic Resources: Options for a Sui Generis System’ (Issues in Genetic Resources No. 6 June 1997), International Plant Genetic Resources Institute.

<sup>45</sup> *Supra* note 40 Explaining that Though TRIPS constitutes the *lex specialis* for dealing with patent issues in the WTO framework, the GATT/WTO jurisprudence on Article XX of GATT is likely to play a role in the interpretation of the said Article. [Citing *India- Patent Protection for Pharmaceutical and Agricultural Chemical Products* case (WT/DS50)]. Article XX (a) and (b) of GATT having a similar structure to Article 27.2, and it is clear that, for the purposes of these provisions exclusions must be objectively justified. [Citing *GATT Analytical Index*, Vol. I, p. 518 *et seq.*]