RSC Law Group’s seminar on IP Enforcement around the World in the Chemical Arts

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London

Presentation by:
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Glivec case, Nexavar Compulsory License, Patent/public health debate & related considerations
Questions the Supreme Court of India considered in Novartis AG vs. Union of India & Others:-

- What is the true import of Section 3(d) of the Patents Act, 1970?

- Whether the Appellant is entitled to get a patent for the betacrystalline form of a chemical compound called *Imatinib Mesylate* which is a therapeutic drug for chronic *myeloid leukemia* and certain kinds of tumors and marketed under the name *Glivec* or *Gleevec*?
Section 3(d) reads as follows:

“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’. 
The amended section 3(d) has its language borrowed from Article 10(2)(b) of European Drug Regulatory Directive, 2004 which defines a “generic medicinal product” as:

“a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of a authorized active substance must be supplied by the applicant.”
Section 3(d) – as explained by the Mashelkar Committee – draws a distinction between “evergreening” and incremental inventions.

The intent of the section was to prevent ‘patent term extension’ by permitting patents for derivatives of known compounds. On the other hand the section sought to benefit the generic drug makers by permitting patents for incremental inventions.

The premise of this provision was that derivatives are structurally similar to the known compounds, hence are presumably functionally also similar. If not, the patent applicants must demonstrate how the derivatives differ from the known substances with regard to efficacy.
Novartis AG Vs. Union of India – challenged the Constitutionality of Section 3(d); Madras HC held Section 3(d) Constitutional


Novartis AG Vs. Adarsh Pharma & Novartis AG Vs. Mehr Pharma & Anr. – Challenging the validity of Exclusive Marketing Rights (EMR) granted to Novartis for “β-Crystalline Salt of Imatinib Mesylate”

Novartis AG Vs. Union of India & Others – Special Leave Petition (SLP), Supreme Court of India, 2013
Does *beta crystalline* form of *imatinib mesylate* pass the test of efficacy under Section 3(d)?

SC: “It is the case of the appellant that the *beta crystalline* form of *Imatinib Mesylate* has 30 per cent increased bioavailability as compared to *Imatinib* in free base form”.

**Extracts from the Patent Application:**

“It goes without saying that *all the indicated inhibitory and pharmacological effects are also found with the free base*, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl] benzamide, *or other cells thereof*. The present invention relates especially to the b-crystal form of the methanesulfonic acid addition salt of a compound of formula I in the treatment of one of the said diseases or in the preparation of a pharmacological agent for the treatment thereto.”
The Beta form significantly differs from the alpha form in terms of the following:

(a) The beta crystal form has substantially more beneficial flow properties and thus results in better processability than the alpha crystal form.

(b) The beta-crystal form of the methanesulfonic acid addition salt is the thermodynamically more stable form at room temperature. Greater stability is thus to be expected.

(c) The beta-crystal form is less hygroscopic than the alpha-crystal form of the methanesulfonic acid addition salt of a compound of formula I.

(d) The lower hygroscopicity is a further advantage for processing and storing the acid addition salt in the beta-crystal form.
Supreme Court on *efficacy*:

On ‘efficacy’ in Section 3(d), Supreme Court held:

“In whatever way therapeutic efficacy may be interpreted, this much is absolutely clear: that the physico-chemical properties of beta crystalline form of Imatinib Mesylate, namely

(i) more beneficial flow properties,
(ii) better thermodynamic stability, and
(iii) lower hygroscopicity,

may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of section 3(d) of the Act, since these properties have nothing to do with therapeutic efficacy
Thus, in whichever way section 3(d) may be viewed, whether as setting up the standards of “patentability” or as an extension of the definition of “invention”, 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) of the Act but that is not to say that Section 3(d) bars patent protection for all incremental inventions of chemical and pharmaceutical substances. It will be a grave mistake to read this judgment to mean that section 3(d) was amended with the intent to undo the fundamental change brought in the patent regime by deletion of section 5 from the Parent Act. That is not said in this judgment.
Bayer developed ‘sorafenib’ (carboxy substituted diphenyl ureas) for treatment of advanced stage kidney cancer

Drug was launched under the mark ‘Nexavar’

Got approval for Renal Cell Carcinoma-RCC (kidney cancer); and additional approval for treating hepatocellular carcinoma-HCC (liver cancer)

Marketing approval received in India in 2008

Entered national phase in India (PCT/US00/000648) on 05.07.2000, patent granted on 03.03.2008

Natco filed an application for Compulsory License on 29.07.2011 (after the minimum prescribed period of 3 years from patent grant; a voluntary licensing request didn’t materialise)

Natco proposed to sell the drug at INR 8800 ($150), whereas Bayer had priced it at INR 2,80,428 (approx. $4500)
Nexavar: Grounds for CL

- Patent Controller heard the CL application on the following grounds:
  - patented invention does not meet reasonable requirements of the public
  - patented invention is not available to the public at a reasonably affordable price
  - patented invention is not worked in India
# Nexavar: Availability & Affordability (India)

<table>
<thead>
<tr>
<th></th>
<th>Total Patients</th>
<th>Demand for 80% of patients</th>
<th>Bottles per month (required)</th>
<th>Bottles Imported in 2008</th>
<th>Bottles Imported in 2009</th>
<th>Bottles Imported in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Cancer</td>
<td>~20,000</td>
<td>~16,000</td>
<td>~16,000</td>
<td>-Nil-</td>
<td>~200 bottles</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td>~8,900</td>
<td>~7,120</td>
<td>~7,120</td>
<td></td>
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</table>

**Sales figures of the drug:**

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<thead>
<tr>
<th></th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
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<tbody>
<tr>
<td>Sales per year (Worldwide)</td>
<td>$165m</td>
<td>$371.7m</td>
<td>$677.8m</td>
<td>$843.5m</td>
<td>$934m</td>
</tr>
<tr>
<td>Sales in India</td>
<td>Nil</td>
<td>nil</td>
<td>Nil</td>
<td>16 crores</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Controller of Patents granted CL on mainly two grounds:
- Nexavar was made available to only 2% of the patients
- It was priced at Rs 2.8 lakhs per month which was unreasonable

ORDER

I hereby grant a compulsory license (hereinafter referred to as ‘license’) under Section 84 of the Patents Act, 1970 to M/s. Natco Pharma Ltd, Natco House, Road No. 2, Banjara Hills, Hyderabad-500033, Andhra Pradesh, India (hereinafter referred to as ‘licensee’) in patent number 215758 (hereinafter referred to as ‘patent’) granted to M/s. Bayer Corporation, 100 Bayer Road, Pittsburg, PA 15205-9741, USA (hereinafter referred to as ‘licensor’) with the following terms and conditions:

a. The price of the drug covered by the Patent, sold by the licensee shall not exceed Rs. 8880 for a pack of 120 tablets, required for one month’s treatment.

b. The licensee shall maintain accounts of sale etc. in a proper manner and shall report the details of sales to the Controller as well as the
Terms of Compulsory License:

Licensor on a quarterly basis, on or before fifteenth day of the succeeding month.

c. The licensee shall have the right to manufacture the drug covered by the Patent only at his own manufacturing facility and shall not in any whatsoever outsource the production.

d. The license is non-exclusive.

e. The license is non-assignable.

f. The licensee shall pay royalty at the rate of 6% of the net sales of the drug on a quarterly basis and such payment shall be affected on or before fifteenth day of the succeeding month.

g. The license is granted solely for the purpose of making, using, offering to sell and selling the drug covered by the patent for the purpose of treating HCC and RCC in humans within the Territory of India.

h. The licensee shall supply the drug covered by the Patent to atleast 600 needy and deserving patients per year free of cost. The licensee shall annually submit in the form of an affidavit the details of such patients, i.e. name, address and the name of the treating oncolgist, to the Office of the Controller of Patents and such report shall be submitted on or before 31st January of the year, in respect of the preceding year.

i. The licensee shall not have the right to import the drug covered by the Patent.

j. The license is for the balance term of the patent.

k. The license does not include any right to represent publicly or privately that the Licensee’s product is the same as the Licensor’s or that the Licensor is in any way associated with the Licensee’s product. The Licensee’s product must be visibly distinct from the Licensor’s product (e.g. in color and / or shape); the trade name
must be distinct, and the packaging must be distinct. The Licensor will provide no legal, regulatory, medical, technical, manufacturing, sales, marketing, or any other support of any kind to the Licensee.

1. The Licensee is solely and exclusively responsible for its product and for all associated product liability. The Licensor, its Directors, Officers, Employees, Agents, and affiliates shall not be held liable in any manner whatsoever for any action of the licensee.

m. The Licensor is free to do whatever it wishes with its residual patent rights subject to the non-exclusive license to the Licensee, and is free to compete with the Licensee and to grant licenses to third parties to compete with the Licensee.
1. Can India limit the scope of patentability to only new chemical entities – is that TRIPS Minus?

2. Can India grant no patents for new usage and dosage of known drugs – is that TRIPS compliant?

3. How is pre-grant opposition & post-grant opposition working out – is their discriminatory treatment for pharmaceutical patents?

4. Is Nexavar the beginning of a surge in compulsory licenses?

5. Is it appropriate to restrict FDI and M&A in pharmaceutical industry?
Please feel free to contact me at LexOrbis at manoj@lexorbis.com if you have questions.

Thank you