THE PATENTS ACT, 1970
(As amended by Patent Act 2005)
&
The Patent Rules 2003
(As amended by Patent Rules, 2006)

In the matter of an application for patent Having no.2485/DEL/1998 made by Boehringer Ingelheim Pharmaceuticals, INC.,of 900 Ridgebury Road, P.O. Box 368, Rigefield, Conn. 06877-0368, United States of America

AND

In the matter of representation of an opposition thereto by Indian Network for People Living with HIV/AIDS(INP+) And Positive Womens network (PWN) India, New Delhi

AND

IN THE MATTER of Opposition u/s 25(1) of the Patents Act, 1970 and rule 55 of the Patent Rules, 2003

Hearing held on 31st August 2007

Present:

Mr. Deepak Mundra,…… Agent for the Applicant
Ms. Ranjana Mehta…… Agent for the Applicant
Sh.Anand Grover…….. Agent for the Opponent
Ms.Shivangi Rai …… **Representative From NPL With HIV/AIDS**

Hearing held on 31st August 2007

DECISION

An application **2485/DEL/1998** titled "Pharmaceutical composition" was filed on 24th August 1998 by Boehringer Ingelheim Pharmaceuticals Inc. hereinafter referred as Applicant through M/s Remfry and Sagar, Attorneys for the Applicant, New Delhi for grant of the Patent. The

invention relates to a pediatric suspension of Nevirapine Hemihydrate used for treating HIV.

The prior art in the application relates to the nevirapine, the active ingredient which is a known agent for the treatment of infection by HIV-1.Its synthesis and use are described in various prior art documents US 5366972, US 5571912, US 556, 9760, EP0429987 and EP0482481.According to the applicants, the stable suspension form of this compound in its hemihydrate form is not disclosed in any prior art documents.

The application was filed with total no. of 6 claims and was published U/S 11A of the Patents Act on 4th March 2005. The application came up for examination and the first examination report was issued on 12/06/06. The examiner raised objections on the grounds of non-patentability u/s 2(1) (j) and definitiveness of the claims. The claims were then amended by the Applicant to comply with the objections.

The present claim 1 reads as follows -

“A pharmaceutical composition consisting essentially of the following constituents in the specified relative range amounts:

Constituent	Range of amount (g/100ml)
Nevirapine hemihydrate	0.1-50
Carbomer934P,NF	0.17-0.22
Polysorbate 80,NF	0.01-0.2
Sorbitol solution,USP	5-30
Sucrose	5-30
Methylparaben,NF	0.15-0.2
Propylparaben,NF	0.02-0.24
Sodium hydroxide,NF	q.s to pH 5.5-6.0
Purified water,USP	q.s ad 100.0 ml

wherein the nevirapine particle size is between about 1 and 150 microns in diameter.

A pre-grant opposition by way of representation was filed by Indian Network for People Living with HIV/AIDS and Positive Women Network hereinafter referred as opponent under section 25(1) of the Patents Act on 9th May 2006 in response to the publication of the application. Consequently, both the parties were heard on 31st August, 2007 as requested under section 25(1) and rule 55(1).

The grounds of opposition relied upon by the opponents are as follows –

(i) Lack of novelty
(ii) Lack of inventive step
(iii) Non-patentability of Claims under Section 25(1)(f)
(iv) Under Section 3(d)
(v) Under Section 3(e)

At the onset the opponents put forth certain propositions of law and facts.

Patent office should give a strict interpretation of patentability criteria as decision of thereof shall affect the fate of people suffering from HIV/AIDs for want of essential medicine.

The opponents put forth the examples of the Novartis v Union of India and others, which affirmed the principle while examining the validity of section 3(d) of the Act. The Honorable Court in upholding section 3(d) against a Constitutional challenge stated" W*e 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 its citizens."

The opponents talked in length about the TRIPS Agreement and were interrupted by the applicant, as these are not being grounds of opposition.

The opponents referred to below mentioned documents to support their statements.

a) Novartis AG & Anrv.Union of India & ors.,W.P.Nos.24759 & 24760 (hereinafter referred as D1)

b) Paris Convention for the Protection of Industrial Property (hereinafter referred as D2)

c) Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective," (hereinafter referred as D3)

The opponent argued that D1 refers to the spirit by which the patentability criteria and section 3(d) was inserted into the Patents Act, 1970, Amendment, 2005. The opponents also put forth the Article 4 bis of the Paris Convention for the Protection of Industrial Property (D2) which states

"*Patents applied for in the various countries of the Union by nationals of countries of the Union shall be independent of patents obtained for the same invention in other countries, whether members of the Union or not. Further "the general terms used in Aricle 27.1[of the TRIPS Agreement] have permitted Member countries to keep different criteria to assess patentability.*

Continuing with D3, which relates to defining patentability and disclosure standards wherein the definitions of novelty and nonobviousness are discussed. Since the TRIPS agreement does not

make it mandatory for the member states to stick to a certain definition, the member states can decide their definitions best suited to their local conditions.

The Applicants did not provide any arguments regarding the above mentioned documents as they agreed to the statements as given above but opined that these documents in no way provided any technical data to establish as to why patents cannot be granted for the said invention.

The Applicant submitted that the section 25(1) of Patents Act, 1970, Amendment 2005 does not have mention this particular criteria as a ground of opposition.

In as such I would not consider the submissions offered in the above paras as a ground of opposition but will consider them facts of law.

I will now consider the grounds relied upon by the opponents in their statement.

Novelty

The following prior art documents were furnished by the Opponents to support the ground of anticipation –

- Angel et al,Electron Microscopy Society of America,1992,132-1327) (hereinafter D1)
- McCrone,W.'"the Microscope"Vol 45,Third Quarter,1997 (hereinafter D 2)
- US Patent no. 5620974 (hereinafter D3)

While going through the articles Angel et al,Electron Microscopy Society of America,1992,132-1327) John A Smoliga- Boehinger Ingelheim-1997 (D1) and McCrone,W.'"the Microscope"Vol 45,Third Quarter,1997(D2) it is well established that it was known that

nevirapine hemihydrate exists as both hemihydrate and anhydrous forms.

US5620974 (D3) describes dipyridodiazepines, methods of making these compounds and a method for preventing or treating HIV infection. Example 12 deals with the method of synthesis of nevirapine. This document discloses that pharmaceutical preparations may be prepared in a conventional manner and finished products may include liquid dosage forms like solutions, suspensions, emulsions etc. and may contain conventional adjuvant such as preservatives, stabilizers emulsifiers flavor improvers wetting agents buffers, salts etc. Infact the document mentions the use of the compound being administered in an aqueous or nonaqueous solution in a pharmaceutically acceptable oil or a mixture of liquids which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood ,thickening agents suspending agents or other pharmaceutically acceptable additives which include tartarate, citrate and acetate buffers, ethanol, polyethylene glycol, polypropylene glycol, EDTA, sodium bisulphate, sodium metabisulphite ascorbic acid, high molecular weight polymers such as liquid polyethylene oxides for viscosity regulation and polyethylene derivatives of sorbitol anhydrides. preservatives like benzoic acid methyl or propyl paraben, benzalkoniumchloride and other qurternary ammonium compounds. The example disclosed for

Parenteral solutions includes :

compound of example 2	5oo mg
tartaric acid	1.5 mg
benzyl alcohol	0.1 by weight
water for injection	q.s.to 1oo ml

for nasal solutions

compound of example 2	100 mg
citric acid	1.92 g
benzalkonium chloride	0.025 percent by weight
EDTA	0.1
polyvinylalcohol	10
water	q.s.to 1oo ml

US5620974(D3) also discusses the use of a parenteral solution with the compound nevirapine for HIV infections. However the cited document does not disclose the said nevirapine hemihydrate 1-150 microns in a suspension form. Also the examples in this document do not show the use of the specific components used in the composition of the alleged invention.

The applicants explained the novel feature of the invention to be the use of suspension of nevirapine hemihydrate maintained between 1 and 150 microns, which has not been cited in any of the documents.

I agree to the contention of the Applicant that all features of claims should be found in single document.

Since no single document cited above do teaches all the features of the claim of the invention; therefore none of the documents challenge the novelty of the invention.
Consequently, the composition claimed is novel.

Inventive step

The opponents provided arguments challenging the inventiveness of the invention. The following documents were relied upon to substantiate the same:

- Angel et al,Electron Microscopy Society of America,1992,132-1327) (hereinafter D1)
- McCrone,W. '"The Microscope" Vol 45,Third Quarter,1997(hereinafter D2)
- US 5620974 (hereinafter D3)
- US 5366972 (hereinafter D4)
- US 5569760 (hereinafter D5)
- Pharmaceutical dosage forms, Lieberman,et al,eds.,vol1(1988),Page 158-Standard textbook on Pharmaceutical dosage forms(hereinafter D6)

Opponent further quoted the :

- Decision of Novartis AG v.Cancer Patients Aid Association in the matter of an application for patent no.1602/Mas/98 filed on July 1998(hereinafter D7)

D1 and D2 discloses that the neviraprine existing in both anhydrous and hemihydrate forms and that during manufacture the hemihydrate is crystallized from solution which may be either be dried at low temperature (35-45^{0}C) and formulated into an aqueous suspension of neviraprine hemihydrate.

D6 teaches that crystal growth and changes in particle size distribution can be largely controlled by employing one or more of the following procedures and techniques:

a) Selection of particles with narrower range of particle sizes

b) Selection of a more crystalline form of the drug

D3 discloses that nevirapine may be administered as medicaments in the form of pharmaceutical preparations which contain nevirapine in association with a compatible pharmaceutical carrier material.

Example 12 deals with the method of synthesis of nevirapine which yields only the anhydrous form. Even though the document says that pharmaceutical preparations may be prepared in a conventional manner and finished products may include liquid dosage forms like solutions, suspensions, emulsions etc. And may contain conventional adjuvants such as preservatives, stabilizers emulsifiers flavor improvers wetting agents buffers, salts etc. Infact the document mentions the use of the compound being administered in an aqueous or nonaqueous solution in a pharmaceutically acceptable oil or a mixture of liquids which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood ,thickening agents suspending agents or other pharmaceutically acceptable additives which include tartarate, citrate and acetate buffers,ethanol, polyethylene glycol, polypropylene glycol, EDTA, sodium bisulphite, sodium metabisulphite ascorbic acid, high molecular weight polymers such as liquid polyethylene oxides for viscosity regulation and polyethylene derivatives of sorbitol anhydrides. Preservatives like benzoic acid methyl or propyl paraben, benzalkoniumchloride and other qurternary ammonium compounds. The example disclosed for

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compound of example 2	100 mg

citric acid	1.92 g
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EDTA	0.1
polyvinylalcohol	10
water	q.s.to 1oo ml

Further more documents D4 and D5 belonging to same patent family disclose about preparation of nevirapine pharmaceutical compositions inter alia suspensions.

D7 states that:
The Patent Office Chennai in examining whether a specific crystalline salt form that was being claimed was inventive over a prior generic disclosure of the free base and all "pharmaceutically acceptable salts thereof" held that because the salt form was obtained from the free base in a customary manner the subsequent claims to the specific crystalline salt formed lacked inventive step.

The applicant has specifically mentioned the use of the nevirapine hemihydrate between 1-150 microns in the composition. However, the specific advantage of this particle size is no where disclosed in the specification. The applicant mentions that this particle size is advantageous to maintain stability of the solution. The applicant claims that this particle size would result in a stable suspension for pediatric consumption. However, the complete specification no where mentions this disclosure.

It leaves me in no doubt that after going through the documents D1 to D7 a skilled person shall be able to arrive at the invention disclosed in this impugned Patent Application.

The alleged invention composition does not specifically have all the components disclosed in the cited documents and whereas all components claimed are known and whereas the established pharmaceutical excepients would produce no other effect and the effect of this disclosed pharamaceutical composition of this instant application would be of the active ingredient only and finally reducing the particle size in he range 1-150 microns by milling or other conventional known methods; therefore shall render this invention disclosed in this application obvious to the person skilled in the Art.

Furthermore, after going through the specification, I also don't see any of the process steps being novel and supported by the description for which monopoly to the applicant may be awarded.

Thus because an aqueous suspension of nevirapine hemihydrate claimed in the Application could readily be prepared in a customary manner by the person skilled in the art the claims lack inventive step.

Therefore the claims of this instant application lacks inventive step.

SECTION 3(d)

The opponents put forth their objections under section 3(d) because they alleged that claims relate to a new form of a known substance without showing the requisite of enhanced efficacy or constitute new uses of already known substances.

Section 3(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 ….is not considered an invention under the meaning of the Act.

Opponent continued that at a minimum the applicant must place on the record two things: 1) data relating to the therapeutic effect of the known substance and b) data relating to the therapeutic effect of the claimed substance. The applicant has failed to place on record either of these items. Firstly, the data presented in the applicant's affidavit shows stability data only for the product claimed in the application. There is no data upon which one can conclude that particle size stability is significantly enhanced over the known substance. Secondly, the data, at most, shows the stability of the nevirapine hemihydrate suspension under various storage conditions. There is no data upon which one can conclude that improved particle size stability translates into better therapeutic effect. Given this lack of data, there is no basis upon which the Patent Controller can conclude that there is the requisite enhancement in therapeutic efficacy.
The opponent also mentioned that the way in which the Madras High Court has defined 'efficacy' the Opponents submitedt that it is impossible for alleged improvements in particle size stability, no matter how comprehensively proved and placed on record, to be sufficient to meet the efficacy requirement of Section 3(d). The Court stated:

"The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, then the patent applicant should show that the substance so discovered has a better therapeutic effect. Dorland's Medical Dictionary defines the expression "efficacy" in the field of pharmacology as " the ability of a drug to produce the desired therapeutic effect, and "efficacy" is independent of potency of the drug. Dictionary meaning of

“Therapeutic” is healing of disease – having a good effect on the body”.

Going by the meaning for the word “efficacy” and “therapeutic” extracted above, what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease/having a good effect on the body. Novartis, Annexure 1 at para 13. Improved particle size stability, at most, means that someone who chooses to manufacture nevirapine in an aqueous solution would benefit from being able to store the medicine for longer periods of time. However, the therapeutic effect of nevirapine, whether in hemihydrate form or anhydrous form, or whether administered in aqueous, tablet, parental or any other dosage form, would remain unchanged. The applicant has failed to place on record any evidence to show that the therapeutic effect of nevirapine hemihydrate in aqueous solution is significantly enhanced over other known forms of nevirapine. As such, Claims 1, 2, and 5 are invalid and fall under Section 3(d).

I have analyzed the above arguments and have come to the conclusion that the product (composition) claims fall under section 3(d) of the Patents Act in the absence of any data for the composition to show enhanced efficacy

Therefore, I conclude that the product claims fall under section 3(d) as they are all a combination of known substances and this section clearly mentions that only if enhanced efficacy can be established such compositions would be allowed to be claimed.

section 3(e)

The opponents alleged that the composition claims are not patentable under section 3(e) of Patent Act 1970 because all the claimed substances obtained by mere admixture resulting only in the

aggregation of the properties of the components thereof and are thus not inventions within the meaning of the Act under section 3(e).The opponents alleged that the applicants had neither in the description nor during the hearing gave any evidence whatsoever to show that the pharmaceutical properties exhibited any properties above and beyond the aggregation of the constituent parts.

The applicants reiterated the fact that there exits a synergy between all the ingredients since these ingredients were not mentioned in any of the cited prior documents.

I agree with the opponent that the applicant failed to show neither in specification nor through the submissions that novel pharmaceutical composition claimed exhibits any of the properties above and beyond the aggregation of the constituent parts.
So claims fall under section 3(e) of the Act and are non-patentable.

In view of the above findings and facts on records, the present application **2485/DEL/1998 is hereby refused to proceed for grant of Patent on the grounds 25(1)(e),read with 2(1)j, and25(1)f read with 3(d),and 3(e) of the Patent Act 1970, The application stands disposed off with no cost to either party.**

Dated.June11,2008
The Patent office,
New Delhi

(N.R.MEENA)
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