

**The Patents act, 1970
(amended by the patents act 2005)
AND
THE PATENT RULES, 2003
(Amended by the Patent Rules 2006)**

In the matter of patent Application no. 896/DEL/2002, filed on 04-09-2002 (Divisional out of Application No. 2174/Del/1998 dated 24-07-1998 & United States Priority dated 25/07/1997)

AND

In the matter of representation by way of opposition U/s 25 (1) dated 27th November 2007 on said application No. 896/DEL/2002.

The Applicants

M/s GILEAD SCIENCES, INC of 333 Lake side Drive, Foster City California 94404, United States of America.

The opponents

M/s Intermed Labs Pvt. Ltd, having its registered address at 77 KIADB Industrial Area, Jigani, Bangalore, 562106, Karnataka, India...

Present:

Sh H. Subramaniam, Sh. G. Natraj, Dr. Ritu Gandhi of M/s Subramaniam, Natraj & Associates, New Delhi, India.....Attorneys for the Applicant.

Sh. S. Majumdar of M/s Majumdar & Co., Kolkata.....Attorneys for the Opponent

Hearing held on September 18th, 2008

DECISION

(A) An opposition was filed under section 25 (1) against the grant of Patent to application no. 896/Del/2002 on 27th November 2007.

The bibliographic and event details of the patent application and opposition U/s 25 (1) are mentioned below:

Sr. No.	Item	Details
1.	Date of application	04.09.2002 ,antedated to the date of filing the parent application No. 2174/Del/1998 dated 24.07.1998 & United States Priority date 25/07/1997
2.	Date of Priority of the application	25/07/1997 (priority from the U.S. applications)

3.	Title of the application	"A nucleotide analog Composition " amended as "A nucleotide analog" (BIS (POC) PMPA FUMARATE ("BPPF") (hereinafter "BPPF")
4.	Utility of the claimed product	BIS (POC) PMPA is a promising agent for the treatment and Prophylaxis of HIV and other viral infections.
5.	Date of publication in the official journal	21 st Jan 2005
6.	Date of issuance of First Examination report	30 th May 2006
7.	Last date of compliance of all the objections	30 th May 2007
8.	Date of submission of finally amended claims.	28 th May 2007
9.	Date of filing of the Representation by the above named party	27 th November 2007
10.	Date of reply by the applicant	16 th May 2008
11.	Date of hearing of the parties by the Controller	18 th Sep 2008
12.	Evidences filed by the opponent	Affidavit from Dr Arvind Natu
13.	Evidences filed by the Applicant	Affidavit from Dr Sundramoorthi Swaminathan

(B) The opponents opposed the Grant of patents under section 25 (1), on the grounds mentioned below: -

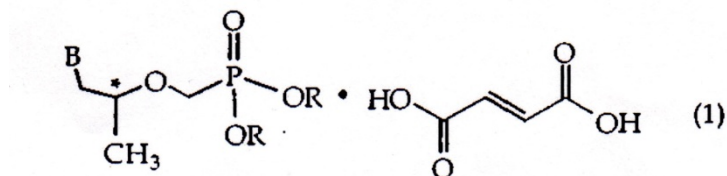
- a. That the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim.
- b. That the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than the applicant's claim.
- c. That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the

matter published as mentioned in clause (a) or having regard to what was used in India before the priority date of the applicant's claim.

- d. That the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim.
1. In any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or
 2. In India or elsewhere, in any other documents:
 - e. That the subject of any claim of the complete specification is not invention within the meaning of this Act, or is not patentable under this Act;
 - f. That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
 - g. The applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to his knowledge.

(C) The initially filed claims are reproduced below (Total 22)

1. A composition of formula (1)



Where B is adenine-9-yl and R independently is -H or -CH₂-O-C(O)-O-CH(CH₃)₂/ but at least one R is -CH₂-O-C(O)-O-CH(CH₃)₂

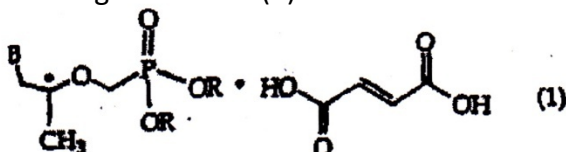
2. The composition of claim 1 wherein both R are -CH₂-O-C(O)-O-CH(CH₃)₂.
3. The composition of claim 1 wherein the composition is a crystalline solid.
4. The composition of claim 1 wherein the compound is enriched or resolved at the carbon atom chiral center (*).
5. The composition of claim 1 having an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0.
6. A composition comprising the composition of claim 1 and an acceptable excipient.

7. A composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl) adenine solution.
8. A composition comprising an (R, S)-PMPA solution at a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/ml (R, S)-PMPA and wherein about 90-94% of the PMPA is in the (R) configuration.
9. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a composition of claim 1.
10. A method comprising contacting bis (POC) PMPA with fumaric acid.
11. The method of claim 10 wherein the fumaric acid is dissolved in 2-propanol.
12. A method comprising mixing a lithium alkoxide with a 9-(2-hydroxypropyl) adenine solution.
13. The method of claim 12 wherein the lithium alkoxide is an alkoxide selected from the group consisting of methoxide, ethoxide, n-propoxide, z-propoxide, n-butoxide, z-butoxide, f-butoxide, neopentoxide, n-pentoxide, /-pentoxide or n-heptoxide, n-heptoxide, 2-heptoxide, n-octoxide, 2-octoxide, typically n-butoxide or z-propoxide.
14. The method of claim 13 wherein the lithium alkoxide is lithium f-butoxide or lithium i-propoxide.
15. A method comprising adjusting the pH of a solution comprising less than about 0.08 g/ml (R,S)-PMPA wherein about 90-94% of the PMPA is in the (R) configuration of a pH of about 2.7-3.5.
16. A composition comprising a tablet containing 9-[2-(R)-[bis[(isopropoxycarbonyl)oxy]phosphinoyl]methoxy]propyl adenine* fumaric acid (1:1), pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate.
17. The composition of claim 16 wherein the 9-[2-(R)-[bis[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl-adenine-fumaric acid (1:1) is crystalline.
18. The composition of claim 16 wherein the tablet contains 75 mg 9-[2-(R)-[bis[(isopropoxy carbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl-adenine >> fumaric acid (1:1), 11 mg pregelatinized starch, 8.8mg croscarmellose sodium, 123.6 mg lactose monohydrate and 2.2 mg magnesium stearate.
19. A product produced by the process of preparing wet granules from a mixture comprising a liquid 9-[2-(R)-[bis(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl-adenine-fumaric acid (1:1) and a pharmaceutically acceptable excipient.

20. The product of claim 19 wherein the liquid is water and the process optionally further comprises drying the wet granules.
21. A composition substantially as herein described with reference to the accompanying drawings.
22. A method of preparing a composition substantially as hereinbefore described with reference to the accompanying drawings.

(D) The finally amended Claims (submitted on 28th May 2007) are reproduced below (Total 9):

1. A nucleotide analog of formula (1).



Wherein B is adenine-9-yl and R independently is -H or -CH₂-O-C(O)-O-CH(CH₃)₂, but at least one R is -CH₂-O-C(O)-O-CH(CH₃)₂.

2. The compound as claimed in claim 1 wherein both R are -CH₂-O-C(O)-O-CH(CH₃)₂.
3. The compound as claimed in claim 1 wherein the compound is a crystalline solid.
4. The compound as claimed in Claim 1 wherein the compound is attached or resolved at the carbon atom chiral center (*).
5. The compound as claimed in claim 1 having an X-ray powder spectrum peak using Cu- α radiation, expressed in degrees 2 θ at about 25.0.
6. A method for the preparation of compound of formula 1 comprising contacting 9 - [2-(R)-[[bis (isopropoxycarbonyloxy) methoxy] phosphinoyl] methoxy] propyl] - adenine with fumaric acid in a manner such as herein described.
7. The method as claimed in claim 6 wherein said fumaric acid is dissolved in 2-propanol.
8. A composition comprising an (R,S)-PMPA solution at a pH of 2.7-3.5 wherein the solution has less than 0.1 g/ml (R,S)- PMPA and wherein 90-94% of the PMPA is the (R) configuration.

9. A Composition comprising a lithium alkoxide and 9-(2-hydroxypropyl) adenine solution for the preparation of PMPA such as herein described.

(E) The opposition will be examined in the light of the amended claims.

Both the parties were heard at length on 18th September, 2008.

The grounds of Novelty (See para B.d above), insufficient disclosure (See B.f) above), prior public use/ prior public knowledge (see B.a. above) and the information required by Section 8 (see B.g above) withdrawn by opponent on the day of hearing.

(F) Discussion about the grounds of Opposition:

(F.1) Ground of Prior Claiming)

On careful consideration of the arguments of both the parties relating to this ground I found that there was no clear support in the United States priority documents relating to D1 i.e. (2076/Del/1997) for maintaining priority of BPPF (Bis (POC) PMPA Fumarate) from date 25/07/1996. In absence of which, the priority for BIS (POC) PMPA Fumarate can not said to be existed from 26/07/1996 as inferred by the opponents from the wordings of claim 1, claim 31 and description in specification of D1 on page 2, 41 and 47.

Therefore the priority for the disclosure of said BPPF (D1) exists from 25/07/1997 which is equivalent to the date of priority for the impugned application No. 896/Del/2002 i.e. 25/07/1997. Therefore D1 in addition to it's priorities fail to establish the ground of prior claiming.

(F.2) Inventive step: Opponents relied on following prior art documents to challenge the inventive step of the invention as claimed in the impugned application:

(F.2.1) Prior art documents:-

(i) Bis (POC) PMPA an orally bio available pro drug of the anti retroviral agent PMPA, Conf, Retroviruses opportunistic infect 1997, Jan. 22-26, 4TH 104 (Abstract no. 214), Bischoberger et. Al., published on 22-26/01/1998 annexed as D2 (hereinafter D2).

- (ii) Salt selection or basic drug, International journal for pharmaceuticals, 33 (1986), 210-217, Gould et. Al. annexed as D3 (hereinafter D3);
- (iii) Material safety data sheets for citric acid and fumaric acid, annexed as D4 (hereinafter D4)
- (iv) Pharmaceutical salts, Journal of pharmaceutical sciences, Jan. 1997, vol. 66 Number 1, Berge et. Al Jan 1977, annexed as D.5 (hereinafter D5).
- (v) CA 2126601 annexed as D6 dated 30/12/1994 (hereinafter D6).
- (vi) US 5498419 March 12, 1996 annexed as D7 (herein after D7).
- (vii) US 5994387 dated 21.11.96 annexed as D8 (hereinafter D8).

(F.2.2.) The opponents have presented various combinations of the documents to establish obviousness of the claimed invention. The same is depicted as under: -

1. D₂ alone
2. D₂ +D₃
3. D₂ + D₅
4. D₂ + D₆
5. D₃ + D₆
6. D₂+D₅+D₆
7. D₇+D₈
8. D₂+D₃+D₄
9. D₆ alone
10. D₇ alone
11. D₈ alone
12. D₂+D₅+D₆
13. D₂+D₇
14. D₂+D₃+D₇
15. D₂+D₅+D₇
16. D₂+D₅+D₈

(F.2.3) The impugned invention is dedicated to solve the problem of instability and low bioavailability of Bis (POC) PMPA (which is known antiviral active substance) if orally ingested. This problem have been solved by providing Fumarate salt of Bis (POC) PMPA, the BPPF.

(F.2.4.) It has observed that D₂ discloses the active agent Bis (POC) PMPA before the priority date of impugned application.

(F.2.5.) Further D₃ provides a rationale to salt selection for basic Drugs. Page 2 provides a table 'FDA SALT FORMS" which list "Fumarate" as a possible salt form used in 0.25% of the basic Drug marketed till 1974. The documents also discloses the reason for selection of various salts including Fumarate salts. These salts preparations of pharmaceutically active compounds develop the improved properties such as improved Bioavailability and the enhanced stability. I observe from the disclosure of D₃ that the disclosure of D₂ and D₃ would motivate a person skilled in the art to develop an acid addition salt including the Fumarate salt.

(F.2.6) I observed that the document D₆ discloses the pharmaceutical acceptable salts of phosphonate nucleotide ester derivatives, which can be orally administered and used as antiviral agents. The basic Drug molecule used in D₆ include PMEA (9-(2-phosphonylmethoxy)-ethyl adenine). The problem solved in the document D₆ if of deficiency of oral absorptivity of the active compound. The compounds being used in the D₆ are having close structural proximity with the parental compounds of impugned invention and both are used in the ester forms. Therefore the skilled person would expect to achieve success for active compounds of impugned invention.

D₆ on page 6 of specification discloses examples of salts including fumarate, which were found suitable for making salt with the parental compounds for obtaining the desired pharmaceutical properties. Therefore the disclosure of D₆ provides sufficient motivation and expectation of success to apply its teachings to the formation of a Fumarate salt of the compound of impugned application with superior physical properties over a free base.

(F.2.7.) D₇ discloses that the Fumarate salt of 4 (diethyl 1-3 (1-methyloctyl-7, 8, 9, 10-tetraphydro-6, 9, 9 trimethyl 6H dibenzo [b, d] pyran-1-ol, 4, dimethyl aminobutyric acid ester is found surprisingly stable, nonhydroscopic, crystalline, stable over prolonged periods of storage

at RT. This document indicates that Fumarate salts are more appropriate to use as pharmaceutical agent unlike other known salts.

(F.2.8.) The applicants contention (in view of the citations as discussed above for evaluating obviousness and inventiveness and also in view of the Opponents reliance on the decision of United States courts of Appeals for the federal circuits in P fizer INC Vs Apotex INC (2006-1261) decided on March 22, 2007 where the Hon’ble Court has defined what is “Unexpected superior property’ and “Reasonable probability of Success”) is that:

- i. The documents relied upon and combined by the opponents for evaluating the obviousness and inventive step of the impugned application are not appropriate as the Fumarate salts as mentioned in various documents discussed above are mere listing of the same along with others like Citrate, Tartarate, Malate etc. and this does not indicate that by considering the same as prior art no skilled person is expected to arrive at the success to carry out the invention;
- ii. The result in the improvement of properties of Bis (POC) PMPA were not expected so with fumarate salt and the success was not expected because of the reason as detailed in the expert evidence by Dr. Sundra Moorthi swaminathan and by the applicant in paragraph 8.41 of reply statement.

The expert evidence by Dr Sundra Moorthi has detailed unexpected results in his expert evidence and thereby the applicants states that Fumarate salt of Bis (POC) PMPA behaved in an unexpected manner and exhibited surprising properties which were not within the perception of the person skilled in the art.

It is stated by them that it was expected that fumaric acid would be a suitable counter ion for Bis (POC) PMPA leading to a stable and useful compound. There were no nucleotide prodrug that were available or approved by FDA at the time of invention of the BPPF.

(F.2.9.) However on perusal of the judgment as referred above , the portion specifically highlighted by the opponents is mentioned below: -

- i. Indeed, rule of law quating unpredictability of patentability, applied in this case, would mean that any new salt – including those specifically listed in the 909 patent itself – would be separately patentable, simply because the formation and properties of

each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable not absolute. Merck, 874 F.2d at 809; In re O. Farrell, 853 f2D 894, 903 (Fed. Cir. 1988).

- ii. Rather, our conclusion here relied on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. We find this case analogous to the optimization of a range or other variable within the claims that flows from the “normal desire of scientists or artisans to improve upon what is already generally known”. In re Peterson, 315 F. 3d 1325, 1330 (Fed. Cir. 2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentage lies in prima facie obvious). In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955), our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious. See also In re Boesch, 617 f2D 272, 276 (C.C.P.A. 1980) (“Discovery of an optimum value of result effective variable in a known process is ordinarily within the skill of the art”).

(iii) It is not inventive to discover the optimum or workable ranges by routine experimentation.” (quoting *Alloer* 220 F.2d at 456)

(iii) Thus, whole patentability of an invention is not negated by the manner in which it was made, “The converse is equally true: patentability is not imparted where ‘ the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.” Merck, 874 F.2d at 809 (quoting In re Dow Chem. Co., 837F. 2d469, 473 (Fed. Cir. 1988).

(iv) The opponents referred to the para 8.42 of their representation that, unexpectedness of improvement of properties’ has been interpreted by the Hon’ble court in the following terms: ‘Evidence of unexpected results can be used to rebut a prima facie case of obviousness Peterson, 315 F.3dat 1330.

([When unexpected results are used as evidence of non obviousness, the results must be shown to be unexpected compared with the closet prior art” (quoting In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed, Cir. 1991).

Another defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be unexpected to be considered as evidence of non-obviousness. In *Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). Thus in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected. *Merck*, 874 F.2d at 808.

In view of all the aforementioned discussion, consideration of reply and argument of the applicant, expert evidence submitted by the applicant and opponents statements, arguments and Evidence and relying on the above-mentioned decision "Federal Circuits in *Pfizer, Inc. Avotex Inc.* (2006-1261; Decided March 22, 2007)" I hereby conclude that the prior art as discussed above for evaluating obviousness and inventiveness affords motivation to the person skilled in the art and brings "reasonable expectation of success" to arrive at the results of the impugned invention and the unexpectedness of improvement of properties in BIS (POC) PMPA on conversion as BPPF as explained by the applicants were expected from such Fumarate salts of pharmaceutical substances. The applicants failed to provide any data and in the impugned Specification which was required to verify the applicant's counsel statement and their expert evidence statement for unexpectedness of improvements over the expected results relating to the properties of Bis (POC) PMPA on its conversion to BPPF.

(F.2.10) Further, it has been stated by the opponent that the claimed BPPF of the impugned application is being marketed in the brand name of "VIREAD". The opponent has also stated that there was 7% and 11% drop in sales of "VIREAD" in the last quarter of 2007 and year ending 2007 as against the sales in 2006 as mentioned the on page 12 of exhibit 4 provided by the applicant. This proves that BPPF does not have enhanced beneficial attributes.

(F.2.11) The opponent provided the document "Approved Draft Labeling of Vired' Page 3 of said document it states that under the heading Pharmacokinetics, sub-heading Absorption states "The oral bioavailability of tenofovir from Viread in fasted patients is approximately 25% and approximately 25% and approximately 40% following a high-fat meal. The opponent then referred to the article "antiretroviral Efficacy and Pharmacokinetics of Oral B Bis (isopropoxy

carbonyloxy methyl) 9- (2-phosphonyl methoxypropyl) adenine in Mice, Antimicrob Agents Chemotherapy 1998 July; 42 (7): 1568-1573” presented by the applicants during the hearing of 2076/Del/1997 WHICH ON PAGE 1572 TEACHES THAT “For bis (POC) PMPA, the oral bioavailability is estimated to be 20% in mice and 30% in dogs.

The opponents stated that the increase in bioavailability by providing BPPF is only 10%.

(F.2.12) The opponents allegation in reference to Expert Evidence para 15.1 and applicants reply para 8.41 that there should be a minimum difference of about 3 times between the PKA value of the group and that of it’s counter ion especially when the Drug substance is a particularly weak acid or base (Exhibit 1 page 427 last sentence) this was nowhere incorporated in the specification of impugned application.

(F.2.13) The opponent also alleged that the difference of about 3 units in the Pka value” which alone has been quoted by the Expert and the applicant has deliberately avoided the further statements on page 2 column 2 which go to say “occasionally, exceptions may be found – where a salt has an acceptable stability despite there being smaller difference in the pKa value.’ Opponent submits that this was the precise situation in the present case and thus the selection of the Fumarate is an obvious choice.

(F.2. 14) the opponents allegation with respect to paragraph 15.9 of applicants expert evidence where the expert has discussed the dimerisation of Bis (POC)PMPA, it was stated that these are mere statements which are bereft of data and scientific reasoning. Similarly with regard to paragram 15.11, it is submitted that no data has been provided in support of the enhanced clinical safety and efficacy of the “Fumarate salt” as claimed by the applicant and merely supported in the form of statements by the expert without any scientific or technical reasoning. Mere statements cannot prove a vital technical advantage which can only be proved by experimental data in the absence of which the one cannot proceed merely on the basis of statements of the expert who on the face of the documents I doubt with regard to his expertise in the concerned area of technology.

(F.2.15) The opponents also drew the attention to page 7 lines 10 to 16 of the complete specification of the impugned application wherein admittedly “Dosages and suitable administration routes to best attack the site of infection are well known

in the art for PMPA. "Determination of proper doses of BPPF is a straight forward matter for the clinician, taking into account the molecular weight of the complexes of this invention and when administering them orally, their bioavailability in animals or as deduced in clinical trails with humans, as well as other factors are well-known to the artisan. " It was further stated that the aforesaid admission of the applicant makes it very clear that BPPF merely facilitates the transport of PMPA to the target site and the compound per se is not efficacious or superior compared to the parent compound PMPA.

(F.2.16) Therefore in view of the abovementioned discussion I observe that the opponents observations are agreeable and I hold that the invention as claimed in the impugned application is obvious to a person skilled in the art and the documents do not show any technical advancement and unexpected advancement of the properties over the known prior art as discussed above in combination D2, D3, D6 and also D2, D6, D7 over the expected properties of such Fumarate salts of pharmaceuticals as discussed in D7. Therefore, the invention as claimed in claims 1 to 9 do not involve any Inventive step.

(F.3) not Patentable U/s 3 (d): It has been observed that the opponent alleges impugned invention falls U/S 3 (d) as the basic compound BIS (POC) PMPA is already known before the priority date of the impugned application. The impugned application has provided the Fumarate salts of the Bis (POC) PMPA which is a salt of known substance" under the definition of sec 3 (d). The applicant had the duty to prove that the Fumarate salt showed significant improvements in properties with regard to efficacy.

I rely on the judgment dated **06-08-2007** of the Hon'ble High Court of Madras in Novartis BS UOI case where the efficacy in r/o the pharmaceutical substance have been defined as therapeutic efficacy which may be proved by providing clinical trails of the newly developed substance.

The relevant part of the above said judgment is reproduced below:

"As we understand the amended section, only declares that the very discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, will not be treated as an invention. The position therefore is, if the discovery of a new

form of a known substance must be treated as an invention, then the patent application should show that the substance so discovered has a better therapeutic effect.... In other words the patent applicant is definitely aware as to what is the "Therapeutic effect of the drug for which he had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for ... The explanation creates a deeming fiction that all derivatives of a known substance would be deemed to be the same substance unless it differ significantly in properties with regard to efficacy.

It has been observed that the impugned application does not depict any clinical trial results to prove that the newly formed fumarate salt is more efficacious than Bis (POC) PMPA in terms of therapeutic effects. Whatever is shown in details as the so-called improvements in the properties, do not amount to an enhancement of therapeutic effect. In the light of all the above discussed I hold that the invention as claimed in the impugned application falls under section 3 (d) and hence not Patentable.

(G) CONCLUSION: Finally in view of the abovementioned discussion I conclude that the invention as claimed in claims of the application No. 896/Del/2002 is not Patentable U/S [1(j)] of the Patents Act (As amended) as being devoid of inventive Step. The claims also falls U/S 3 (d).

(H)O R D E R:- In the light of the above discussion I refuse to grant the patent on applicable No. 896/Del/2002. No order for cost.

Dated: 30/07/2009

Sd/-
(HARDEV KARAR)
ASST. CONTROLLER
OF PATENTS & DESIGNS