BEFORE THE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

THE PATENTS ACT, 1970
The Patents Rules, 2003

(SECTION 25(1) and RULE 55)

In the matter of the Indian Patent Application No.396/DEL/1996 filed on 26th FEBRUARY 1996 filed by GILEAD SCIENCE INC. of 333 Lakeside Drive, Foster City California 94404 United States of America.

AND

In the matter of opposition under section 25(1) to the grant of patent thereto by M/s. MEDITAB SPECIALITIES PVT.LTD, an Indian Company at 31,Khimji Meghji House, 11/15 Issaji Street, Vadgadi, Mumbai, Maharashtra India.

GILEAD SECIENCE INC. USA.....The Applicant

MEDITAB SPECIALITIES PVT.LTD INDIA.....The Opponent

Presents in the hearing:

(1) Mr. G. Nataraj---------- Agents for the Applicant
(2) Dr.Gopakumar G.Nair----------Agent for the opponent
(3) Mr. Douglas Lopez----------An associate of agents for opponent
(4) Ms Surabhi Sinha----------An associate of agents for the applicant
(3) Dr. Rachna Nandwani----------Examiner of Patents and Designs

THE DECISION

Facts of the case:

1. M/S Gilead Science, Inc.(hereinafter referred as applicant(s)) a US company, through their agent M/S Remfry & Sagar, filed their patent application No 396/Del/1996 on 26th FEBRUARY 1996 as WTO (**mail box**) application under section 5 of the Patents Act 1970 for the grant of product patent for their invention entitled "Carbocyclic Compounds" claiming the priorities of three US applications namely,08/395,245, 08/476,946 and 08/580,567 filed on 27th February 1995, 6th June 1995 and 29th December 1995 respectively. However, the request for examination was filed on 17thJune 2005 when the Patents Act 1970 was amended by the Patents (Amendments) Act 2005 by M/S Subramanian, Nataraj & Associates, who replaced Remfry & Sagar as the applicant's agent.On the receipt of the examination request the application was examined and First Examination Report (FER) vide office letter396/DEL/1996/13464dated17th March2006 was sent to the applicant's agent M/S Subramanian, Nataraj & Associates. The said examination report *inter-alia* contained the following main objections namely,

(1) Subject matter of claim 1 does not constitute an invention for lack of novelty, inventive step/non-obvious and Industrial applicability under section 2(1)(j) of the Patents Act, 1970 in view of citations (separate sheet attached).

1. WO-A9206691
2. WO-A9116320
3. EP-A 0539204
4. Nature (London)(1993), 363 (6424), 418-23 (1993), Von Itzstein, Mark, Et. al, "Rational design of potent sialidase-based inhibitors of influenza virus replication".
5. Chandler; J. Chem. Soc. Perkin Trans. 1 (1995), 1189-1197.
6. Ogawa; J. Chem. Soc Chem. Comm, 3, 1687-1696 (1992)
7. WO 91/16320

8. Woods, J.M. et. Al, (1993) 4-Guanidino-2,4-Dideoxy-2, 3-Dehydro-N-Acetyl neuraminic Acid is a highly effective inhibitor both of the sialidase (Neuraminidase) and of growth of a wide range of influenza A & B viruses in vitro. Antimicrobial Agents and Chemotherapy, July 1993, 1473-1479.

9. P.M.Colman, "Influenza virus neuraminidase; Structure, antibodies, and inhibitors", Protein Sci-(1994) 3: 1687-1696.

10. Poirrette, R.A. et al, (1994). Structural similarly between binding sites of influenza sialidase and isocitrate dehyetrogenase; Implications for an alternative approach to rational drug designs, Protein Sci.3: 1128-1130.

11. Patent No.5360817 (US).

12. Pub. No.0539204 Al (EPO)

(2). All claims fall with the scope of such clause of section 3(e), 3(d) & 3(i) for claims 38, 39, 69, 70.

(3). Claims 9-16, 40-68, 7273 define a plurality of distinct inventions.

(4). Claims are unnecessary repetition of claim 9-16.

(5). Claims are large in number.

(6). Claims do not sufficiently define the invention.

(7). Claims are not fairly based on the matter disclosed in the specification.

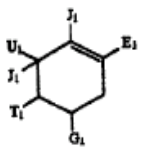
(8). Claims are not clear in respect of as indicated therein.

(9). Claims are not clearly worded.

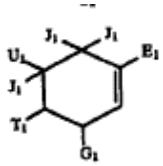
2. The instant application originally disclosed 73 claims out of which claims 1 to 37, 40, and 71 were related to a composition comprising of a compound of formula (I) or (II), claims 38,39 and 72 related to a method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with the composition and claims 41 to 68 related to a compound of formula I(Carbocyclic compound) and claims 69 and 70 were related to a method of using a compound of the

formula 281 wherein the method comprises treating compound 281 with R_5-X_1-H and claim 73 to a process of preparation of a composition comprising of compound of formula(I) or(II).

3. The applicants re-filed the documents along with the response to the official objections vide their letter No. GN/hs/RST/0938 dated March 2, 2007 and No. GN/hs/396/DEL/1996 dated16th March 2007 and also reduced the number claims to 44 from 73 which were originally filed. Thereafter the patent office did not take any action on the documents in view of pendency of representation by way of opposition. The last date to put the application in order for grant was to expire on 17th March 2007.Now the claims 1 to 42 and 44 on the records as on the last date i.e.17th March 2007 are related to compounds of formula (I) or (II) and claim 43 to a method of preparation of compound as claimed in claim 42.



Formula (I)



Formula (II)

4. As mentioned above, in the meantime M/s. MEDITAB SPECIALITIES PVT.LTD, an Indian Company (herein after referred as opponent(s)) filed the representation on 21st February 2006 to oppose the grant of patent u/s 25(1) on the grounds as mentioned in clause (b) to (g) of sub-section (1) of section 25 of the Patents Act 1970. The opponents further filed an amended representation on 16th March 2006. The applicant filed their reply statement on 7th April 2006 which was supported by the evidence of Dr. Sundaramoorthi Swaminathan. The applicants also requested the patent office to allow the opposition proceedings to go concurrently with the examination proceedings. This was the reason why patent office could not proceed further. The applicants filed the reply statement of the amended representation on 3rd May 2006.Accordingly a hearing was finally fixed on

15th October 2007after considering the request of the applicants. However the opponents also filed a rejoinder along with affidavit of Dr.P.Aruna Sree (a patent professional) on 12th October 2007 i.e. just before the date of hearing with a copy of the same to the applicants as same was acknowledged and opposed by the agents for the applicants vide their letter dated 12th October 2007 with a request not to take the same on the record since there was no provision in the patent law for filing of such rejoinder in the pre-grant opposition. The hearing was held as scheduled and attended by both the parties along with their representatives.

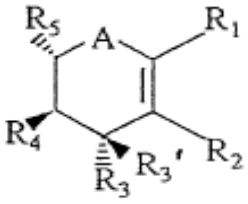
Submissions/arguments of the opponents

5. The opponents in their representation including the amended one relied upon the grounds of (a) prior publication,(b) prior claiming,(c)Obviousness and lack of inventive step, (d) not an invention within the meaning of the Act or not patentable under the Act,(e) Insufficiency of description and (f) failure to disclose the information to the controller under section-8 or has furnished the information which was false to his knowledge.

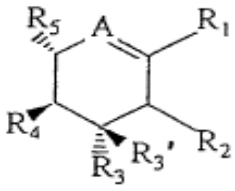
6. For, the grounds of prior publication and prior claiming, the opponents have relied upon Indian patent applications namely 2791/DEL/98 dated 17th Sept.1998(marked as Annexure-I)and 1132/DEL/1999 dated 20th Sept.1999(marked as Annexure-II)and international patent application under Patent Cooperation Treaty (PCT) namely,PCT/AU91/00161dated 24th April1991 which was published as WO91/16320 dated 31st October 1991(marked as Annexure-III) wherein the subject matter of the alleged invention is said to have been disclosed and published. The opponents stated that Indian applications as mentioned above have common contents and claims as to the impugned application which have been published on 01/07/2005 and are in public domain therefore not patentable. They further stated that the disclosures and claims made in the form of "Markush" claims with very wide range of groups, side claims and substituents, chemical entities with

similar and even same structures and same groups in impugned application are disclosed and claimed in prior cited documents and publications. This is evident from the facts that the claimed invention in impugned application specifically excludes by way of disclaimers those compounds that are known in the prior art disclosures, in particular that disclosed in WO91/16320 and W092/06691 due to being anticipated or obvious under the law of United States. The Biota has 74 patents under national phase of PCT in member countries as family. Accordingly the claimed subject matter in the opposed application lacks in novelty and stands anticipated by said prior publications and prior grant.

7. With regard to the ground of obviousness and lack of inventive step, the opponents have relied upon the same prior art document No.WO91/16320, **marked as Annexure-III** entitled "derivatives and analogues of 2-Deoxy-2.3-didehydro-N-accetyl neuraminic acid and their use as Antiviral agents". They have stated that the disclosure and claims are obvious from the disclosures in the prior art particularly as disclosed in the Biota application wherein the compounds of the following structure formulae have been disclosed and claimed;



(I)

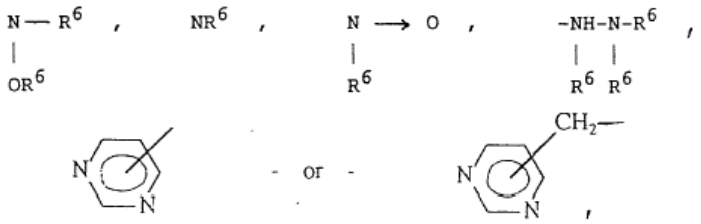


(Ia)

Wherein general formula (I), A is oxygen, carbon or sulphur, and in general formula (Ia), A is nitrogen or carbon; R^1 denotes COOH, P (O)$(OH)_2$, NO_2, SOOH, SO_3H, tetrazol, CH_2CHO, CHO or $CH(CHO)_2$, R^2 denotes H, OR^6, F, Cl, Br,CN,NHR^6, SR^6 or CH_2X.wherein X is NHR^6,halogen or OR^6 and R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl

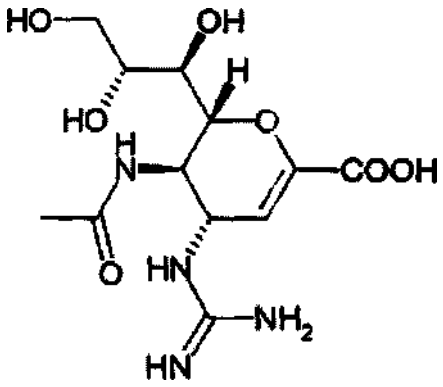
group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a COOH group;

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, CN, NHR^6, N_3, SR^6, =N-OR^6, OR^6, guanidino,



R^4 denotes NHR^6, SR^6, OR^6, $COOR^6$, NO_2, C $(R^6)_3$, CH2$COOR^6$, CH_2NO_2 or CH_2NHR^6

R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$, where Y is O, S, NH or H, and successive Y moieties in an R^5 group are the same or different. The opponents specifically referred to the compound "Zanamivir", which is 1992 molecule and having following structural formula.



8. For the ground of not an invention or not a patentable invention, the opponents contended that the alleged invention being a 'product' is not an invention and not patentable under the Patent Act, 1970 (as amended upto 2005) in India. The priority date for this application is 27th February 1995. The product claimed herein as an invention, does not qualify for grant of a

product patent in India as the product has already been invented prior to 1.1.1995. The appropriate tests for qualifying for a product patent status has already been done prior to 1.1.1995, even though the priority application has been filed on 27.02.1995(refer to the now repealed section 24B of the Patent (Amendment) Act, 2003).Further, Article 70(3) of TRIPS Agreement provides that "there shall be no obligation to restore protection to the subject matter which on the date of application of the agreement has fallen into the public domain". They further submitted that since the section 5(2) and the section 24B have been deleted, the examination of the patent application can only be done under the Patent Act, 1970 as amended upto 2005, as it stands amended as on date, under which there is no provision for granting a product patent for an application filed prior to 1.1.2005, as the present amended Act could not consider an application filed prior to 1.1.2005 for a product patent. They have further contended that compounds covered under the impugned application are pharmaceutically acceptable salts/derivatives/esters of compounds disclosed and claimed in the earlier application of Biota (WO91/16320) where the structure of the compounds is also similar including identical therapeutic activities without any enhancement in the efficacy and therefore are not patentable under section 3(d) of the Patents Act 1970 which 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 opponents also contended that the method of inhibiting, method of treatment and other methods claimed in claim 3 to 7 are not patentable under section 3(i) of the patents Act 1970

9. On the ground of insufficiency of description, the opponents contended that the complete specification of this application does not clearly describe the invention as the applicants have made extra-ordinary wide, wild and vague claims to confuse and mislead, without experimental support and justification. Further there is no description of the method to be performed in support of the infinite number of structures claimed and their therapeutic activities have not been supported by experimental evidence.

10. The opponents also relied upon the ground of failure to submit information under section 8, or has furnished the information which in any material particular was false to his knowledge and contended that the applicants have failed to furnish information under section 8.Especially those information which disqualifies this product patent claim of the compounds disclosed have been withheld by the applicant. It was further contended that the "product" under claim for patent is a pre-1995 molecule and is not eligible for a product patent. Relevant information which disqualifies the grant of a product patent has not been filed by the applicant and has been withheld. Further, the details of prosecution in other jurisdictions have not been filed in India, by the applicant.

Apart from the above ground the opponents also mentioned some further grounds but they in substance are merely the repetitions.

Submissions/arguments of the applicants:

11. The applicants, while replying to the representation of the opponents, submitted in their preliminary submission that the representation filed by

the opponents is frivolous, vexatious, has no merit and has been filed merely for the purpose of delaying grant of patent on this application and also based on grounds that are not available under Section 25(1) of the Patents Act, 1970.They also submitted that amended representation by the opponent was filed without any justifiable cause just to delay the grant of patent as the provisions of section 25 do not permit the opponents to keep on filing the representation *ad infinitum* particularly when the controller has issued a notice to the applicant to file their reply.

12. As regards prior publication, the applicant contended that the citation of Indian patent applications namely 2791/DEL/98 and 1132/DEL/1999 are not relevant as the priority dates of both the applications are later than the priority date of the instant application. It was also submitted that the present invention is novel and is not the same as WO91/16320. Moreover WO92/O6691 relates to heterocyclic and not carbocyclic compounds and what is taught by EP 632,048 is neither similar nor equivalent to present invention. They also alleged that the opponents have quoted extensively from the applicant's specification and even mere glance at the structure of cited compound and compounds of formula I and II of claim 1 of the present invention shows the significant difference. Further, although in WO91/16320, passing reference includes carbocyclic compounds, there is no specific example of carbocyclic NAIs in the specification. Besides, the R^5 side chain is hydrophilic in nature, whereas, the present invention has a lipophilic chain at the R^5 position of the cyclohexene ring. Increasing the overall lipophilicity of the carbocyclic compound balances the effects of the polar functional groups present in the molecule. Hence, by balancing the lipophilicity and water solubility the overall oral bio-availability of the composition is enhanced. The cyclohexene ring of the present invention is chemically and enzymatically stable in the human GI tract. The novel non-polar interactions are the key in achieving high binding affinity of the cyclohexene based NAIs. They further alleged that the opponents have

failed to produce any evidence to substantiate their allegations. The applicants also submitted that their invention is novel as USPTO and EPO have also granted patent to them taking into consideration of each citation same citations were also cited in the International Search Report (ISR).

13. As regards inventive step, the applicants contended that the present invention is not only novel but also has an inventive step with reference to the cited documents. They also submitted that the question of obviousness can only be determined on the basis of expert evidence by a person skilled in the art which opponents have failed to do so. It was also submitted that compositions of formula 1 or 1a in WO91/16320, in passing reference includes carbocyclic compounds; however there is no specific example of carbocyclic NAIs in the specification. Besides, the R^5 side chain is hydrophilic in nature, whereas, the present invention has a lipophilic chain at the R^5 position of the cyclohexene ring. Increasing the overall lipophilicity of the carbocyclic compound balances the effects of the polar functional groups present in the molecule. Hence, by balancing the lipophilicity and water solubility the overall oral bio-availability of the composition is enhanced. The cyclohexene ring of the present invention is chemically and enzymatically stable in the human GI tract. The novel non-polar interactions are the key in achieving high binding affinity of the cyclohexene based NAIs. The invention also relates to a novel method of making the compounds having a cyclohexene ring which has carbon at group "A" position and YR^6 at R^5 is not hydroxyl group. This makes the claimed compound *in vivo* non-hydrolysable.

It was further submitted that Zanamivir does not anticipate the instant invention as Zanamivir (4-guanidinao-Neu5Ac2en) is a dihydropyran ring (i.e. a non carboxylic ring) with polar glycerol moiety and guanidino group as two of its side chains whereas the present invention is based on a cyclohexen scaffold. Among other changes, the instant invention replaces the polar glycerol moiety of sialic acid based inhibitor

with lipophilic side chains and guanidino group of zanamivir with an amino group. Further, Zanamivir, which can be administered nasally, is a slow inhibitor. The instant invention addresses and overcomes the disadvantages of the cited art and therefore the entire submissions on the ground of lack inventive steps are denied.

14. Regarding the ground of not an invention and non patentable invention, the applicants submitted that the invention claimed by them is novel as not anticipated by prior art citation and involve inventive step. Regarding patenting of product, the applicants contended that the instant application is a WTO (mail box) application filed on 26th February 2006 claiming the priority date of 27th February 1995(after 01-01-1995) and therefore the chemical and pharmaceutical products are patentable in India. They also argued that the present invention is neither claiming a method of treatment nor any mere derivatives of the cited compounds (Biota).They further stated that the compound of prior art suffer from deficiencies such as short –lived half life and unsatisfactory limitations in the manner of dosage brought on by the biological instability of the compounds. However the NAIs of the present invention have enhanced efficacy over the known NAIs and have elevated potency, substantial oral bioavailability (>15%) and clinically acceptable or minimal toxicity compared to known compounds. Examples 119-122 of the specification show the enhancement of the efficacy of the new inventive compounds which are significantly superior to known compounds. They stated that the present application claims novel compounds and novel composition and not simple admixtures. In fact, the complete specification clearly mentioned that what is being claimed are derivatives, salts, solvates, and resolved enantiomers and purified diastereomers of the novel compositions and compounds and not of known prior compounds disclosed in prior art documents.

With respect to utility, the applicants stated that utility of an invention is not a ground available to the Opponent under Sec 25(1) of the

Act. The very factum of opposition to this application is a proof of utility. The compounds of the prior art suffer from numerous deficiencies like short-lived half life and biological instability of the compounds. The present invention provides improved and less costly methods for synthesis of neuraminidase inhibitors and provides such inhibitors having higher potency, substantial oral bioavailability (>15%) and clinically acceptable or minimal toxicity compared to known compounds. Examples 119-122 of the present specification show the enhancement of the efficacy of the new and inventive compounds. Moreover, the claimed compounds have high oral bioavailability and biological half-life and thus can be administered orally; it is not necessary to administer them by intrapulmonary or intranasal rout.

The applicants further submitted that the allegation of the opponents that the present invention is a mere admixture is completely unscientific as instant application claims novel compounds and compositions which are synergistic in nature(description contained on pages 144-148) and section 3(e) does not apply to the compounds *per-se.*

15. The applicants denied the allegation of the opponent with respect to insufficiency of disclosure and contented that complete specification provides sufficient support to any person of ordinary skill in art to work the invention and particularly the examples thereof supported by experimental evidences provide sufficient guidance to a person of skill in the art to form various salts, solvates, derivatives, and resolved enantiomers or purified diastereomers of basic compounds of the invention. As regards, utility of the invention the applicant stated that the same has been given in detail in pages 144-155 of the description. The opponents have not mentioned which part of the specification is not fully enabled and no proof has been provided by the opponents about the non-workability of the invention. Further, they alleged that the opponents have failed to specify which example and scheme described by the applicants has failed to give claimed

results under physical and chemical conditions and therefore the objection of the opponent is malicious and very vague.

16. With respect to the ground of failure to submit information under section 8, or has furnished the information which in any material particular was false to his knowledge, the applicants contended that the allegation of the opponents is false and no material information has been withheld or falsely disclosed by the applicants.

In additions to above reply the applicants in general also replied the further grounds of opposition as alleged by the opponents whom I have already stated to be repetitive and hence the reply by the applicants in that respect is also repetitive.

Consideration of grounds/submissions/Arguments of both parties

17. Having given a brief of the submissions made by the opponents on each of the grounds as well as the reply thereto given by the applicants, now I shall consider each of the grounds as mentioned below, in the light of the arguments in the hearing, written submissions submitted by both parties and facts of the case including their replies and evidences of the experts. However, before considering each of the grounds, let me consider one issue relating to filing of rejoinder by the opponents just before the hearing date. The agents for the applicants opposed such rejoinder vide their letter dated 12th October 2007 on the ground that there is no provision in the patent law for such filing and more so because it was filed at last moment just before the hearing that too without any leave of the controller and also because it was filed even beyond the time limit prescribed under Civil Procedure Code. In my opinion such kind of rejoinder must not be encouraged to be allowed particularly when other party is put under disadvantage unless and until it is absolutely necessary and natural justice so demands. I have gone through the contents of the rejoinder and found that the agents for the opponents have merely reiterated the same points

which have been submitted in the representations except one or two points which are in fact a matter of records such as prosecution history of corresponding US applications in USPTO and copy of federal register etc which I think have no relevance to the case. It has also been found that the opponents had also submitted an affidavit purporting to be expert evidence deposed by Dr.P.Aruna Sree who is currently a patent expert and has five years of experience in synthetic organic chemistry apart from holding the master degree in organic chemistry. In that affidavit Dr.Aruna Sree has not highlighted or thrown any light as to why the instant invention is not novel and why alleged invention is obvious to a person skilled in the art, rather reiterated merely the same thing what has been stated by the opponents in their representation and therefore the affidavit offers no help and is of no consequence. Since the proceedings under section 25(1) are similar to summary proceedings to expedite the matter, such rejoinder must be rejected. Even if I consider it same offers no help. Having said so, now I shall consider each ground of the opposition as relied upon by the opponents.

(a) Prior publication: For the ground of prior publication, the opponents have relied upon Indian patent applications namely 2791/DEL/98 dated 17th Sept.1998(marked as Annexure-I)and 1132/DEL/1999 dated 20th Sept.1999(marked as Annexure-II), international publication under Patent Cooperation Treaty (PCT) WO91/16320 dated 31st October 1991(marked as Annexure-III), W092/06691 published on 30th April 1992 and EPO publication 0632048A1wherein the subject matter of the alleged invention is said to have been disclosed and published. At the outset I agree with the applicants that cited Indian applications namely 2791/DEL/98 dated 17th Sept.1998 and 1132/DEL/1999 dated 20th Sept.1999 are not at all relevant for the purpose of prior publication since their priority dates are later than the priority date of the instant application as same was filed in

India on 26th February 1996 claiming 27th February 2005 as priority date of corresponding US Application which was the convention country on that date.

During hearing Shri Gopakumar Nair, the agent for the opponents contended that Biota, which claims a Markush structure of compounds encompasses the compounds as claimed in the opposed application. In other words the invention of Biota (WO91/16320) is the Genus while alleged invention of the applicant is a mere Species. If A is substituted with carbon, the ring of Biota also becomes carbocyclic in nature. I have gone through these documents and the invention disclosed in the complete specification of the application under opposition and found that PCT document W092/06691 is not fully relevant as it discloses only A=O(pyran ring) but not carbon atom. Similarly EPO publication 0632048A1 is also not relevant. Most relevant document appears to be WO91/16320 where the some of compounds as claimed therein admittedly fall within the scope of the present invention which is the fact, applicants have also admitted and that is also one of the reasons why the applicants have made a specific disclaimer about those compounds. On pursuing the specification and the documents submitted by the opponents, it is observed that despite some similarities, there are some differences in the features namely, (a) the formula I or Ia (WO91/16320 known as Biota) covers all those compounds where , **A** = oxygen, **carbon** or sulphur or even nitrogen but in fact disclosed mostly compounds of pyran ring**,** whereas Formula I or II of the present invention covers only those compounds of the Carbocyclic ring where J1 is attached to Carbon atom, that means where A= carbon in formula 1 of Biota are covered within the scope of the invention but it is capable of including other compounds where A= oxygen, sulphur or nitrogen,(b) Carbon is a linker atom equivalent to U1 such as CH_2 in case of Biota whereas Oxygen, nitrogen or sulfur are linker atoms in U1

substituent of the instant invention and (c) there are some difference in other substitutions.

A test relating to anticipation to invalidate a subsequent invention in view of the disclosure made in the prior published document was stated by Lord Westbury, L.C in *Hills v.Evans*. "TERREL on the Law of Patent, Twelfth Edition (para 292). According to this test, "the antecedent statement must, in order to invalidate the subsequent patent, be such that a person of ordinary knowledge of the subject would at once perceive and understand and be able practically to apply the discovery without the necessity of making further experiment ….the information….given by the prior publication must, for the purposes of practical utility, be equal to the given by the subsequent patent". Applying the above test of anticipation and information available on the record, I found that the information given in the prior art documents such as WO91/16320, WO92/06691 or even EPO 0632048A1 is not equal or same to that given in the specification of the instant application as there are differences between them as pointed above and for that reason alone I hold that the opponents have failed to prove the lack of novelty on the ground of prior publication.

(b) Prior claiming: This ground was although mentioned in the representation but no document was submitted in support of it except those mentioned for prior publication. As mentioned above, none of them is relevant for this purpose and also this ground was not pressed by the opponents during the hearing therefore needs no consideration as appears to have been dropped.

(c) Obviousness or lack of inventive step: In support of this ground, the opponents have relied upon same document namely (i) PCT Publication No.WO91/16320 of Biota **marked as Annexure-III.** During hearing Shri Gopakumar Nair, the agent for the applicants made following observations,

(a) In the prior art compounds when “A” is carbon, the basic ring structure of compound formula 1 or 1a of the prior art is same as that of compounds as claimed in instant application.

(b) Biota on page no.7 describes that derivatives of prior art compounds can be modified at the C1 carboxyl function to obtain the esters. Therefore esterification of carboxyl group is a direct teaching in the prior art document to obtain the esters of carboxylic group at E1of the alleged invention and this makes the invention obvious.

The evidence of Dr. Aruna Sree could not throw any light on this issue except merely reiterating the same what was stated by the opponents in the representation.

I have also gone through the reply submitted by the applicants and also the evidence of Dr. S Swaminathan who has about 40 publications to his credit apart from his qualification and experience in the area of current field of technology. The applicants in their reply statement as well as in the evidence have made following observations. The similar observations were made by Shri Nataraj during hearing also.

(a) The neuraminidase inhibitors (NAI) of the prior art suffers from deficiency such as short lived half life and unsatisfactory limitations in the manner of dosages brought on by the biological instability of the compounds.

(b) The present invention discloses and claims the compounds of cyclohexene scaffold whereas the prior art discloses heterocyclic and aromatic ring based NAIs. The prior art has a passing reference only to include Carbocyclic compounds but there is no reference towards preferred groups or specific examples of carbocyclic NAIs.

(c) The compounds of present invention have a lipophilic chain at equivalent position of cyclohexene ring and the balancing the lipophilicity and water solubility enhances the bio-availability of the composition.

(d) The NAIs of the present invention are having higher potency, substantial oral bio-availability and clinically acceptable minimal toxicity as compared to known compounds. The examples 119-122 of the present specification teach the enhancement in the efficacy of the novel compounds.

As far as Indian patent law is concerned, the term “inventive step" has been defined in section 2(1)(ja) of the Patents Act,1970 "as a feature of the invention that involves technical advance as compared to the existing knowledge or having economical significance or both and that makes the invention not obvious to a person skilled in the art". Therefore for proper investigation as to whether the alleged invention involves inventive step or not is to find out (a) the closest prior art or existing knowledge on the date of priority of the alleged invention (b) Is there any technical advancement or economic significance or both made by the alleged invention as compared to the existing knowledge or prior art and (c) whether such technical advancement or economical significance is obvious to a person skilled in the art. If the answer is affirmative, in that situation the invention will be obvious and lacking inventive step and if the answer is negative, the invention will be non-obvious and involving the inventive step. Further, the obviousness is also a question of facts which must be decided objectively and for deciding this question; all the relevant circumstances should be taken into account.

The Hon’ble Supreme Court of India in the landmark Judgment in case of ***Biswanath Prasad Radhey Shyam vs Hindustan Metal Industries*** (AIR 1982 SUPREME COURT 1444), while laying down the principles about the patentability of invention particularly the subject matter and inventive step stated that “it is a necessary qualification of a craftsman that he should have the Knowledge and ability to vary his methods to meet the task before him. A tailor must cut his cloth to suit the fashion of the day and any monopoly that would interfere with the

craftsman's use of his skill and knowledge would be intolerable as it may be only a normal development. A patentable invention, therefore, must involve something which is outside the probable capacity of a craftsman- which is expressed by saying it must have 'subject matter' or involve an "inventive step".

The Hon'ble court further stated that another test of inventive step is "Had the document been placed in the hands of a competent craftsman (or engineer as distinguished from a mere artisan),endowed with the common general knowledge at the 'priority date', who was faced with the problem solved by the patentee but without knowledge of the patented invention, would he have said, "this gives me what I want". To put it in another form: "was it for practical purposes obvious to a skilled worker, in the field concerned, in the state of knowledge existing at the date of the patent to be found in the literature then available to him, that he would or should make the invention the subject of the claim concerned ?"(Halsbury, 3rd Edn, vol. 29, p. 42 referred to in Farbwrke Hoechst vs. Unichem laboratories).

In fact "the philosophy behind the doctrine of obviousness is that the public should not be prevented from doing something which is merely an obvious extension or workshop variations of what was already known at the priority date. Accordingly the skilled man is treated as having access to every sample of the prior art, and must be considered as sufficiently interested in the information which he is deemed to have to consider in practical application whether he would have done so or not"**[Patent law by P.Narayanan, fourth Edition 2006,para 16-82 and page 410 last paragraph]**.

It is also a settled law that "while considering the issue of obviousness that relevant comparison is not between the preferred embodiment of the invention claimed and the prior art. If any embodiment within the scope of

claim is obvious, then claim is invalid" (para 310, TERREL on The Law of Patent, 12th Edition, 1971, pp 126- 127).

In the light of above guiding principles, submissions made by both parties and description in specification of the instant application, I am of the opinion as under-

(a) The applicants appears to have selected carbocyclic ring compounds having known enzymatic inhibition activities out of the invention disclosed in prior art document of Biota (WO91/16320) which has disclosed the compounds having heterocyclic ring as well as carbocyclic ring(due to Markush kind of structure). In fact, the applicants in their submissions have also admitted that prior art did disclose the carbocyclic compounds although no specific reference of such compound has been given. It is also clear from the document that all possible compounds where A is either carbon or sulphur or oxygen or nitrogen possess enzymatic (neuraminidase) inhibition activities. Therefore, the activities of carbocyclic compound as well as heterocyclic compounds which may be derivatised out from general formula as disclosed in Biota document as neuraminidase inhibition have already been identified and known before the priority date. In view of this, it is clear that change in the ring system of the compounds does not affect their enzymatic (neuraminidase) inhibition activities.

(b) It is also a fact on the record and also admitted by the applicants in the specification that the certain compounds of alleged invention which the applicants have disclosed in the specification (due to Markush kind of structure and claims) are being anticipated by and overlapped with the compounds as disclosed in the prior art (WO 92/06691, EPO Publication No. 0539204A1 and WO91/16320) mentioned by them in the specification **as identical** (See renumbered page No 8). In other words, the compounds of the prior

(c) It is also a fact on the record as well as within the common knowledge of any chemist that if A is selected as carbon in the formula 1 or 1a as disclosed in Annexure-III(WO91/16320) then what they called a pyran ring compounds, becomes carbocyclic ring compounds which are same as that of the applicants.

(d) It has also been disclosed in Annexure-III on page no.7 that compounds of formula 1 or 1a can be modified at the C1 carboxyl function (at E1of the alleged invention)to obtain the esters. Therefore the esterification of carboxyl group is well known in the prior art document to obtain the esters of carboxylic group. It is also disclosed on the same page that "it will be appreciated by those skilled in the art that pharmaceutically acceptable derivatives of the compounds of formula 1 may be derivatised at more than one position. Hence, it is quite obviously possible to provide further substituents at various positions of formula 1 or 1a of the prior art by the person skilled in the art to obtain the compounds having desired effects. Further, it is also clear from the comparison of the documents and specification of the alleged invention that some of the corresponding substituents such G_1,T_1 of the instant invention are common to R^3 and $R^{3'}$, R^4 of BIOTA.

(e) The article of Mark Von Itzstein et al, *Rational design of potent sialidase-based inhibitors of influenza virus replication,* Nature, Vol. 363, 3 June 1993 (page 420 right hand column, lines 1-4 of the section titled "Inhibition of influenza virus sialidase"**)** discloses numerous compounds that bind neuraminidase. Although this document was not relied upon by the opponents but it was sent to

(f) It is also known that –O- and –CH2- are classical bioisosteres which are well known to a skilled person and person skilled in the art would substitute linker –CH2- with linker –O- in order to decrease the hydrophilicity so as to increase the lipophilicity to achieve the desired results. The process of bioisosterism is well known to be used in molecular modification. Therefore in view of the above it appears that the applicants have replaced certain substituents of the known compounds by known manner and known techniques which could be within the grasp of the person skilled in the art.

(g) The applicants as well as Dr. S Swaminathan on the other hand stated that the examples 119-122(the present specification) teach the enhancement in the efficacy of the compounds. However on close examination of these examples, it is observed that they indicate only the enzymatic inhibition activities of the compounds of the alleged invention where various compounds of formula I or II have been screened off for their inhibition activity and no comparison is made with known compounds.

(h) The applicants statement is that the neuraminidase inhibitors (NAI) of the prior art suffers from deficiency such as short lived half life and unsatisfactory limitations in the manner of dosages brought on by the biological instability of the compounds. The increased lipophilicity and water solubility of the compounds of the present invention enhances the bio-availability of the composition so that

(i) On reading the specification, I have no doubt that the applicants have made derivatives of the known compounds by changing or substituting at various positions to achieve the desired results such as oral administration of drug, enhanced half life etc. Applying the problem-solution approach as followed by European Patent Office as well as European Board of Appeals in order to judge inventive step or obviousness, one would tend to conclude that the applicant's alleged invention by having solved the problem of prior art meets the requirements of establishing inventive step. While evaluating the obviousness issue, above mentioned approach is also one of the approaches followed by Indian Patent Office. However for considering the issue I do not find any supportive evidence in the specification by means of comparative data or by way of examples which would have supported the inventive merit of the alleged invention. Therefore in my opinion simply saying or alleging of the improvements would not help the cause of the applicants. For this, I rely upon the decision of European Board of Appeal (T-0133/01) where said board held that alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underline the claimed invention. This needs comparative tests to meet the criteria which include the proper choice of comparative compound to be taken from the state of the art.

(j) The applicants alleged advantage that the compounds of the present invention are orally bio-available and can be dosed orally and therefore not required to be administered by intrapulmonary or intranasal rout appears to be illusioned as they themselves have stated on page 144 of the specification that compounds of the present invention are administered by any rout appropriate to the conditions to be treated which include oral, rectal, nasal, topical (including buccal and sublingual) vaginal and **parenteral** (including subcutaneous,intramuscular, intravenous, intradermal, intrathecal and epidural) and the like. Therefore, it is difficult to agree with the applicants that making the compounds of the alleged invention capable of oral administration would have been inevitably necessary in solving this technical problem.

(k) On the basis foregoing discussion and submissions made by the opponents it appears that the changes, modifications or substitutions as carried out by the applicants in the compounds of the prior art as disclosed in Biota document are well within the skill of the person in pursuit of knowledge by using the knowledge from prior art with a reasonable expectation of success and carrying out routine experiments to achieve the desired results. Therefore in a case where Markus kind of claims are claimed, if main features of the alleged invention are obvious modifications, the entire invention must be held obvious, also when some compounds of prior art have been considered as anticipation by the applicants themselves, the other modifications within same frame work of structural design of compound must be considered obvious if not considered as anticipation

In view of the above observations, I am of the opinion that alleged invention is devoid of any inventive step and therefore obvious to the person skilled in the art.

(d) Not an invention under the Act: The opponents have again alleged that the invention is devoid of inventive step due to lack of technical advancement and economic significance. Since I have already dealt with this issue, it does not require any further consideration. I will consider separately the contention of the opponents that the product claimed herein does not qualify for grant of a product patent in India as the product has already been invented prior to 1.1.1995.

(f) Not a patentable invention under section 3(d) of the Act: I have gone through contention of the opponents in the representation and the reply of the applicants. The contention of the opponent that the recitation of pharmaceutically acceptable salt, solvates and derivatives, dissolved enantiomers and purified diastereomers in the claimed composition are clearly not patentable under section 3(d) of the Act particularly in view of the explanation thereto , is not tenable. If the compound is novel, its derivative and other forms are patentable and can be claimed in same application. However, what is not patentable under the provisions of section 3(d), is the new form of known substance such as polymorphs metabolites, isomers, complexes and other derivatives of known substances unless they differ significantly in properties with regard to efficacy.

Although, the applicants in the instance application have made several disclaimers in the claims as well as in the description regarding the known compounds (in WO 92/06691 and WO91/16320) in an attempt to avoid anticipation but failed to give any comparison with respect to enhancement in enzymatic inhibition activities of both kinds of compounds in the specification(compounds of prior art and compounds of the alleged invention).I agree to certain extent with the applicants view that the compounds of the alleged invention are of carbocyclic or cyclohexen scaffold whereas compounds as disclosed in the prior art are of only pyran ring. But the point is that prior art document (BIOTA) has also disclosed a broad range of compounds including carbocyclic compounds in addition to

heterocyclic compounds, the fact which the applicants have also admitted. Moreover, their enzymatic (neuraminidase) inhibition activities were already identified at that time and no change in the activities was reported due to change in the ring structure. Therefore they remain to be neuraminidase inhibitors as their inhibition activities are not changed due to change in the ring structure. Since BIOTA document has already identified the neuraminidase inhibiting activities of such compounds they remain to be same class of compounds, let them be either carbocyclic or heterocyclic. Accordingly I feel that the opponents are right in saying that the compounds of the present invention are merely Species of Genus of compounds disclosed by BIOTA which has also mentioned that compounds of their invention could be carbocyclic as well. Therefore the compounds of the present invention have to be considered in fact as derivatives of known compounds.

The applicants agents argued that the neuraminidase inhibitors (NAI) of the prior art suffers from deficiency such as short lived half life and unsatisfactory limitations in the manner of dosages brought on by the biological instability of the compounds. They also argued that the NAIs of the present invention are having higher potency, substantial oral bio-availability (>15%) and clinically acceptable minimal toxicity as compared to known compounds. In addition to this the compounds of present invention have a lipophilic chain at equivalent position of cyclohexene ring and the balancing the lipophilicity and water solubility enhances the bio-availability of the composition. According to the applicants, the examples 119-122 in the specification teach the enhancement in the efficacy of the novel compounds. On pursuing the specification one can know that these are the statements made by the applicants in the specification either as objectives of the invention or as drawbacks of the prior art compounds but these statements are neither supported by any experimental data based on the alleged invention nor by any comparative data to establish the validity

of the facts in respect of efficacy, bioavailability or higher potency as claimed by the applicants. I made it very clear that I am not talking about the clinical data but comparison data based on the experiments done at the time when the alleged invention was made while comparing the bioavailability, shelf life or potency with respect to known compounds at that time.

I have also gone through these examples (119-122) and observed that examples 119-121 indicate only the enzymatic inhibition activities of the compounds of the alleged invention where various compounds of formula I or II have been screened off for inhibition activity whereas example122 indicates some reaction schemes which are being performed but none of them indicates either enhancement in their efficacy or about their higher potency or bioavailability as compared with the compounds known in the prior art. The applicants also argued that the compounds of the alleged invention can be administered orally and therefore it is not necessary to administer them by intrapulmonary or intranasal routes. But on page 147 of the specification it is stated that the formulations are suitable for intrapulmonary or nasal administration including other routes of administration, it means that such routes are not eliminated rather oral administration is achieved by suitable modifications or substitutions of the compounds known in the prior art based on the information available in the prior art documents using well known techniques which is the common function in the drug designing mechanism by a person endowed with the common general knowledge. This assumption of mine is reaffirmed by the disclosure on page 24-25 of the specification where protecting groups are used to protect certain groups of the prior art compounds in order to make them suitable for oral administration due to hydrolytic cleavage *in vivo*. Further, prior art document namely EP Publication-0539204A1 (claiming Zanamivir or Relenza as this document was referred to in FER) on page-4 discloses that the formulations can be presented as discrete units in the

form of capsules, cachets or tablets which are normally taken orally and on page-5 it is mentioned that the formulations can also be prepared for sustained release. Therefore in my opinion the alleged invention has failed to meet the requirements under these provisions in order to be patentable. In other words the alleged invention as claimed and described in the instant application attracts the provisions of section 3(d) of the Patents Act 1970.

Since the applicants, during examination, have amended the claims by deleting the claims relating to method of inhibiting the activity of neuraminidase and compositions, the objections of not patentable under section 3(i)and 3(e) as alleged by the opponents have become infructuous.

(g) Insufficient disclosure: The opponents have contended that the description and claims are vague and wide to confuse and mislead, without experimental support and justification. Further there is no description of the method to be performed in support of the infinite number of structures claimed and their therapeutic activities have not been supported by experimental evidence. The agent for opponents in the hearing also argued that the specification has failed to meet the requirement of enablement as there are numerous compounds claimed in Markush form and also supported their arguments by submitting the judgment of United States Court of Appeal for Federal Circuits in *Pharmaceutical Resources Inc* and *Par Pharmaceutical Inc* vs. *Roxane Laboratories Inc*. On the other hand the applicants denied the allegations of the opponents and contented that complete specification provides sufficient support to any person of ordinary skill in art to work the invention and particularly the examples thereof supported by experimental evidences provide sufficient guidance to a person of skill in the art to form various salts, solvates, derivatives, and resolved enantiomers or purified diastereomers of basic compounds of the invention.

In order to satisfy the requirement of sufficiency of description, the applicant for patent is required to satisfy at least following three conditions, namely (a) the complete specification must describe an embodiment of the invention claimed in each of the claims,(b) the description must be sufficient to enable those in the industry concerned to carry it into effect without making further invention or experiments and (c) the description must be fair i.e. it must not be unnecessarily difficult to follow**[Patent law by P.Narayanan, fourth Edition 2006,para 16-175 and page 463]**.Since the sufficient disclosure of the invention to the public through the specification is the basis of the patent grant, the controller[being the custodian of the public rights]has to consider the rights of the public so that the public can exploit the invention commercially[without doing further experiments]after the expiry of the term of patent. Therefore the Controller has to ensure that the description and claims provided in the specification are clear and succinct and not ambiguous to be understood by the ordinary skilled person.

On pursuing the specification, one can understand that the applicants have given certain disclaimers in the description as well as in the claims to exclude the compounds specifically described in the prior art (WO 92/06691 and WO91/16320) in an attempt to avoid anticipation. The contention of the applicants that such disclaimers are not barred under any provision of the patent law, are not tenable. I understand that there is no specific provision in the patent law to prevent them from making such disclaimers and in fact disclaimers are allowable in practice in order to define clearly the scope of the invention. The disclaimer is allowed for the purpose of preventing the subsequent patentee from alleging that his invention is wider than he is entitled to claim **[Patent law by P.Narayanan, fourth Edition 2006,para 7-33 and page 176]**. Further, whereas a disclaimer can be used to make an inventive teaching which overlaps with

the state of art novel, it can not make an obvious teaching inventive (T 170/87(OJ1989, 441).

Moreover, the applicant is under statutory duty to disclose the best method of performing the invention which is known to him and for which he is entitled to claim protection and also to have claims defining the scope of the invention for which protection is claimed. In other words it is the duty of the applicant to draw out his own territory clearly and without any ambiguity to let the public know the exact boundary of the invention so that trespassers can be prosecuted for their act of trespassing. However, the applicants' case is that they are identifying the alleged invention by saying that except XY and Z compounds (by making disclaimers) rest is theirs out of (A-Z). But what the applicants were supposed to do was to emphatically claim that out of (A-Z) only A, B, C, D and F were theirs. Therefore the applicant must claim his own invention for which he is entitled rather than claiming the entire world and making some disclaimers about something which he is aware to be known. This is a kind of ambiguity in claims which put the public in difficulty to understand clearly the exact nature of the compounds covered by the alleged invention as well as the exact nature of the disclaimed compounds and therefore disclaimers should have been made cautiously by clearly demarcating the line between what is inventive and what is known in the prior art and not just to make an obvious teaching inventive.

In fact, the claim or claims in the specification define the monopoly or protection which the applicant claims as his own exclusive right and therefore demarcate(s) the boundary of the patent right of the applicant(patentee) or a fencing surrounding the invention from other information or knowledge available in the world in the field of the invention. Accordingly, the function of the claims is to show with conciseness, precision, and accuracy as to what the invention in respect of which monopoly is sought. Further the applicants have given a list of thousands

_____ in the specification from pages 40 to 142 with various combinations and permutations leaving the public at its own imagination and peril to verify such compounds which further make the description ambiguous. In fact what was expected from the applicants was to describe their own inventive features precisely rather than making ambiguous statements in the specification.

Further, the applicants in the specification(page-2 and 3) have stated that neuraminidase inhibitors (NAI) of the alleged invention exhibited lengthy biological half lives as compared to known compounds. It is further stated that are also having elevated potency, substantial oral bioavailability (>15%) and clinically acceptable or absent toxicity compared to known compounds. It has also been stated by the applicants that the method of synthesis of neuraminidase inhibitors of the alleged invention is less costly. However there is no supportive data or evidence in the specification by means of any comparative data in the examples to establish these facts and in the absence of which, the description in the specification, in my opinion, must be held insufficient.

Accordingly I am of the opinion that the description of the invention is ambiguous and ambiguity amounts to insufficiency.

(h) Failure to furnish information under section 8: The opponents have relied upon the ground that applicants have failed to provide all the information regarding the prosecution in other jurisdiction and other details of their corresponding foreign applications till the grant of patent to the Controller in writing from time to time and also within the prescribed time under section 8 of the Act, which the applicants have denied. The agents for applicants also submitted in the hearing that applicants have regularly kept the Patent Office informed of the status of all corresponding foreign applications including their prosecution histories and are continuing to do so. This can be seen from a mere perusal of the records of this application submitted to the Patent Office. I fully agree with the

submissions of the applicants since the opponents have not brought any information to the notice of the controller or any evidence even until the date of hearing or even till date which the applicants might have concealed and not furnished. The applicants have also submitted the revised information in form 3 on 27th November 2007 along with petitions under rule 137 and 138 of the Patents Rules 2003, giving the latest information about the corresponding applications filed abroad which the office has already taken on the record. I therefore hold that the opponents have failed to prove this ground in the absence of any evidence.

(i) Application not qualified for mail box as WTO application: The opponents contended in the representation and their agent Mr.Gopakumar Nair also argued in the hearing that the "product" under claim for patent is a pre-1995 molecule on which the appropriate test had been conducted and therefore is not eligible for a product patent as India is not obliged to grant product patent on such molecules. On the other hand the applicant as well their agents denied the allegations. Mr.Nataraj in the hearing argued that such ground is not available in the pre-grant opposition under section 25(1) of the Act. I fully agree with the applicants that this is not the ground which is available under section 25(10 of the Patents Act 1970 as amended. If the opponents felt that the claimed products are pre 1995 molecule, then they should have agitated under the ground of prior publication, prior claiming or prior public use which I have already considered and given my opinion in the preceding paragraphs. In view of the above, I do not consider necessary to give any further opinion on this issue except that the applicants have claimed the priority date of corresponding US application validly within the prescribed time. Further the applicants had also filed the instant application after 1st January 1995 when the Patents (Amendment) Act 1999 amending the Patents Act 1970 came into force by providing the provision under section5(2) to receive the

applications for product patents for inventions relating to pharmaceuticals and agrochemicals.

18. After having considered all the circumstance of this case, representations for opposition, reply statements of the applicants, expert evidence in their support, written submissions and arguments in the hearing made by both parties and also my discussion and findings as mentioned above, I am of the opinion that the alleged invention as clamed in the claims is not only obvious to person skilled in the art and lacking in inventive step but also insufficient and ambiguous as described in the specification. The alleged invention is also not patentable invention under the provisions of section 3(d) of the patents Act 1970 for the reasons as explained above. In view of the above circumstances, I dispose of the representation by refusing this application to proceed further for the grant of patent thereon under rule 55(6) of the Patents Rule 2003.

Dated this 23rd day of March 2009

(Dr. K.S. Kardam)
Deputy Controller of Patents & Designs.

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