

under section 5(2) of the Patents Act 1970 for the grant of product patent for their invention entitled "Carbocyclic Compounds" claiming the priorities of three US applications No. 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 17th June 2005 (after 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 receipt of said request, the application was examined and First Examination Report (FER) was issued vide office letter No. 396/DEL/1996/13464 dated 17th March, 2006 to M/S Subramanian, Nataraj & Associates, the applicant's agent. 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 the following citations (separate sheet attached).

a) WO-A9206691

b) WO-A9116320

c) EP-A 0539204

d) Nature (London)(1993), 363 (6424), 418-23 (1993), Von Itzstein, Mark, Et. al, "Rational design of potent sialidase-based inhibitors of influenza virus replication".

e) Chandler; J. Chem. Soc. Perkin Trans. 1 (1995), 1189-1197.

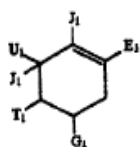
f) Ogawa; J. Chem. Soc Chem. Comm, 3,1687-1696 (1992)

g) WO 91/16320

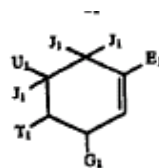
h) Woods, J.M. et. Al, (1993) 4-Guanidino-2,4-Dideoxy-2, 3-Dehydro-N-Acetyl neuraminic Acid is a highly effective inhibitor both of the sialidase (Neuraminidase) and of growth of a wide range of influenza A & B viruses in vitro. Antimicrobial Agents and Chemotherapy, July 1993, 1473-1479.

- i) P.M.Colman. "Influenza virus neuraminidase; Structure, antibodies, and inhibitors", Protein Sci-(1994) 3: 1687-1696.
 - j) Poirrette, R.A. et al, (1994). Structural similarity between binding sites of influenza sialidase and isocitrate dehydrogenase; Implications for an alternative approach to rational drug designs, Protein Sci.3: 1128-1130.
 - k) Patent No.5360817 (US).
 - l) Pub. No.0539204 A1 (EPO)
 - (2). All claims fall within 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, 72-73 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) (as indicated below), claims 38,39 and 72 were 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 were 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 R₅-X₁-H and claim 73 to a process of preparation of a composition comprising of compound of formula(I) or(II).
- 3.** The applicant's agents 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 of 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 filed under section 25(1) of the Patents Act 1970 as amended in 2005. However, 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 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, during the prosecution of said application, M/S CIPLA LIMITED, an Indian company (herein after referred as opponent(s)) filed the representation on 6th September 2006 to oppose the grant of patent u/s 25(1) of the Patents Act 1970. The applicants filed their reply statement on 5thMay, 2006 alongwith the evidence of Dr.Sundaramoorthi Swaminathan in their support. Accordingly hearing was finally fixed on 17th OCTOBER 2007 after considering the request of the applicants, which was attended by both parties along with their representatives. The matter was further heard on 23rd October 2007 due to incompleteness of proceedings on 17th October 2007 as agreed by both parties.

Submissions/arguments of the opponents

5. The opponents in their representation relied upon the grounds namely, (a) prior publication, (b) prior public knowledge or prior public use in India, (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 file convention application within 12 months. Further, the opponents appear to have also given the detail analysis of the claims as well as description of the alleged invention. The details of each ground are given in the subsequent paragraphs.

6. With regard to lack of novelty on the ground of prior publication, the opponents have relied the following documents namely,

(a) WO 95/07920 published on 23rd March 1995(**Exhibit-7**)

(b) The international patent application No.PCT/AU91/00161 under Patent Cooperation Treaty(PCT) dated 29th April1991 and published on 31st October 1991under International publication number WO91/16320(**Exhibit-8**)

(c) WO 92/06691 published on 30 April 1992 (**Exhibit-9**)

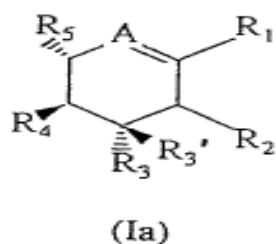
(d) EPO publication EP 0539204 A1 published on 28 April 1993 (**Exhibit-10**)

(e) An article by Mark von Itzstein et al, "*Rational design of potent sialidase-based inhibitors of influenza virus replication,*" published in Nature, Vol. 363, 3 June 1993 page 420 (**Exhibit-11**)

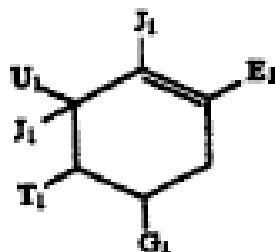
(f) EP 632,048 (**Exhibit-13**)

The opponents stated that above mentioned prior art is most relevant and discloses numerous compounds that bind neuraminidase and have a nucleus as claimed in opposed application. Although, the Applicants have referred to the above relevant prior art in the opposed application on page 2 but have cleverly used negative language on page 7 at line 10 and throughout the claims to exclude the same. According to the opponents, while the applicants may argue that this amounts to a disclaimer of the prior art from the claims made in the opposed application, it should not hide the fact that the structure of the compound(s) claimed were already disclosed or embraced by the prior art and are, therefore, simply derivatives thereof which lack any novelty or inventive step. It was further stated that out of the prior art as mentioned above, WO91/16320 (**Exhibit 8**) and the Von Itzstein article (**Exhibit 11**) are the most relevant which negate any novelty for the compound(s) as claimed in the opposed application. The compound of Formula 1(a) of claim 1 in WO91/16320(**Exhibit-8**) is

represented below, wherein the various functional groups may be represented as A = C, R₁ = COOC₂H₅, R₂ = H, R₃ = NH₂ and R₄ = NHCOCH₃



(WO91/16320)



(Formula I of opposed application)

In claim 1 of the opposed application, formula (I) as given above, when substituted by the various functional groups such as E₁ = COOEt, J₁ = H, G₁ = NH₂, U₁ = O(CH(C₂H₅)₂) and T₁ = NHCOCH₃ represents the compound structure for Oseltamivir as shown above. If one replaces the groups A, R₁, R₂, R₃, R₄ by the functions claimed in formula (Ia) of the prior art ('320), it reveals a structure that has very little difference to that claimed in the opposed application. The only difference between the structures claimed in '320 and opposed application resides in the group U₁, whereas U₁ forms a C-O linkage with the ring whilst the corresponding R₅ of WO91/16320 forms a C-C linkage with the ring. Indeed, this is clearly admitted by the Applicants in the opposed application on page 7 at line 28 onwards. This close similarity with the prior art is best shown by comparing compound 38 (page 162) and compound 203 (page 174) in the opposed application with the compounds claimed in the said prior art. Technically speaking, the class of compounds claimed in the opposed application were simply selected, or more accurately derived from the prior art, in particular '320, and as a result they should not be considered novel.

The opponents further contended that the applicants in their application for patent have claimed the priority of application (not applications) filed in United States so first of all the multiple priorities

should not be allowed despite disclosing the details of multiple US applications in the form. Secondly the name of one of the inventors namely Norbert Bischofberger was not disclosed in the first convention application (U.S Patent No. 5866601). Thirdly, the claims made in the opposed application almost entirely correspond to the claims set out in U.S Patent 5763483(29th December 1995) and not U.S Patent No. 5866601(6th June 1995 claiming the priority date of 27th February 1995(abandoned application)). As a result, the Opponent believes that the Applicants have, repeatedly, throughout Form 2A, failed to make clear which of the convention applications it is claiming priority from for the opposed application. Fourthly, since the applicants have broadened the scope of the invention in U.S Patent 5763483 as compared to U.S Patent No. 5866601, the priority of the later application should not be allowed and as result any intervening prior art between 27th February 1995 and 29th December 1995 should be considered relevant.

7. As regards prior public knowledge or prior public use in India, the opponents have merely mentioned this ground in the representation but it was neither corroborated by any evidence nor contested during hearing and therefore in my opinion be taken as withdrawn or non-contested.
8. As regards obviousness, the opponents have relied upon the following documents, namely;
 - (a) An article by Morris, et al, *An integrated approach to the selection of optimal salt form for a new drug candidate*, International Journal of Pharmaceutics 105 (1994) pages 209-217, (**Exhibit 5**)
 - (b) An article by Gould, *Salt Selection for basic drugs*, International Journal of Pharmaceutics, 33 (1986) pages 201-217, attached as **Exhibit 6**,
 - (c) WO 95/07920 published on 23rd March 1995(**Exhibit-7**)
 - (d) The international patent application No.PCT/AU91/00161 under Patent Cooperation Treaty(PCT) dated 29th April 1991 and published on 31st October, 1991 under International publication number WO91/16320 (**Exhibit-8**)
 - (e) WO 92/06691 published on 30 April 1992 (**Exhibit-9**)

- (f) EPO publication EP 0539204A1 published on 28 April 1993(**Exhibit-10**)
- (g) An article by Mark von Itzstein et al, "*Rational design of potent sialidase-based inhibitors of influenza virus replication,*" published in Nature, Vol. 363, 3 June 1993 page 420 (**Exhibit-11**)
- (h) EP 632,048 (**Exhibit-13**) published on 4 January 1995,

The opponents have contended that the alleged invention does not meet the requirement of section 2(ja) of the Act as it lacks in inventive step in view of the disclosure in the complete specification of the opposed application on page 7 at line 28 onwards and also in view of the disclaimer on page 7 at line 15 that the compositions and compounds claimed exclude compounds that are obvious under Article 103 of the United States Code Title 35 (**Exhibit 12**). They further contended that the slight modifications made by the applicants in the opposed application over the prior art as attached in **Exhibits 8-11**, in particular '320 (**Exhibit 8**) and the article attached as **Exhibit 11**, do not amount to an inventive step or a technical advance, because it is common practice of organic chemists who are concerned with the preparation of new drugs to take some interesting or clinically desirable pharmacological properties as a model and to study the effect of making relatively small changes in its structure. By replacing the oxygen pyran ring by a -CH₂- moiety, which is the only minor difference between opposed application and the prior disclosed art, the applicants could still expect similar properties from the parent compounds of the prior art disclosed in **Exhibits 8-11** and its ring equivalents as claimed in the opposed application.

The opponents further stated that the minor modification in group U₁ of the opposed application by the applicants was pre-conceived and obvious in order to prepare a carbocyclic to obtain a hydrophobic group which would then make the compound more lipophilic so as to allow for salts to make it more bio-available and to retain the properties of the original molecule. Given that the claimed invention is to provide an oral neuraminidase

inhibitor, anyone versed in the art would recognize that to achieve this outcome one of the first steps would be the replacement of the oxygen of the pyran ring by a -CH₂ -moiety or prepare a carbocycle. Indeed, page 3 at lines 20-26 of '320(**Exhibit-8**) effectively discloses the formula for obtaining a carbocyclic of neuraminidase inhibitor as claimed in the opposed application by showing that the ring system can be adopted with either oxygen, carbon or sulphur in order to achieve preparation of an NAI.

The Opponent further stated that they are well versed and familiar with the field of pharmacology and antiviral pharmaceutical substances, and therefore strongly believe that the steps claimed by the applicants in the opposed application are common to medicinal chemistry. For example, hydrophobic drugs such as nitroglycerin or steroids are known to cross the mucosal membrane rapidly, the former being well known for its bioavailability. Similarly, the replacement of the polyol groups, as claimed by the applicant, by a hydrophobic group is also known to be an obvious choice for the skilled medicinal chemist and within drug development in order to establish whether it will have the right physical properties to improve uptake. Therefore, the claimed 'inventive steps' taken by the applicant to obtain an oral neuraminidase inhibitor should be considered obvious to a skilled person/a team of skilled persons or at least obvious to try given the expectation that a carbocyclic ring would be easier to modify for oral bioavailability. The above contention, as alleged by the opponents, is further supported by the fact that numerous prior art is available which demonstrate how orally delivered hydrophobic drugs, such as protease inhibitors, have included a -CH₂-replacement to achieve the desired effect.

The opponents further contended that the applicants implicitly claim the pro-drug of Oseltamivir by claiming "pharmaceutically acceptable salts, solvates and derivatives thereof and resolved enantiomers and purified diastereomers of the compounds claimed and the active acids esters and amides to obtain the active metabolite. However, it has long been common

knowledge in the pharmaceutical industry that the conversion of a lead (main) molecule into a pharmaceutically acceptable salt can result in numerous advantages, including improved dissolution rate and bioavailability. Various prior art exists which teaches a systematic, expeditious approach to finding the optimal salt for any given new drug candidate in order to improve the overall properties of a drug. For instance, Morris, et al, *An integrated approach to the selection of optimal salt form for a new drug candidate*, International Journal of Pharmaceutics 105 (1994) pages 209-217, (**Exhibit 5**) discloses an integrated, three-tiered approach to selecting the optimal salt for any given new drug candidate. Starting from a pool of seven possible salts, the authors proposed an approach by which the least time-consuming experiments were conducted in the first tier, and the more time-consuming experiments were conducted as more and more candidates were eliminated in the earlier tiers. Using this approach, the authors concluded that the entire salt selection process could be completed within 4-6 weeks or less and easily be adopted into the drug development program. This view is further substantiated in the Article by Gould, *Salt Selection for basic drugs*, International Journal of Pharmaceutics, 33 (1986) pages 201-217, (**Exhibit 6**). Therefore such claims do not amount to an inventive step and are obvious in light of the arguments as stated above.

Similarly for the active metabolite of the compound(s) of the alleged invention, as claimed and disclosed in Scheme 28 and Example 94, there can be no inventive step. In fact, any claim for the obtaining of the active metabolite is anticipated and obvious from the disclosure in the prior art WO 95/07920 (**Exhibit-7**) and EP 632 048(**Exhibit 13**), which describe the acids as metabolites of the respective esters and which have obviously been incorporated by the applicants, as explained on page 25 at line 30 of the specification.

The opponents also stated that the applicants have already admitted on page 24 at line 1 and throughout page 25 of the opposed application that

the obtaining of the relevant acid addition salts and esters to achieve oral bioavailability have already been disclosed and explained in the prior publications of EP 632 048(**Exhibit 13**), and WO 95/07920 (**Exhibit-7**). Therefore, in light of the prior art, the claim for pharmaceutically acceptable salts and active acid esters to improve the bioavailability of the alleged invention is not only anticipated but also lacking in inventive step. Further, the applicant have failed to show how the preparation of the salts and esters claimed amount to an improvement over the art and in relation to the invention claimed.

9. With respect to the ground of not an invention and not patentable, the opponents contended that the alleged invention as claimed and disclosed in the opposed application does not constitute an invention under section 2(1) (j) due to lack of novelty and inventive step in view of the prior art as mentioned above and also not patentable under section 3(d) and 3(e) of the Act as the word "invention" has been defined as "*a new product or process involving an inventive step*", while "inventive step" to be "*a feature of an invention that involves technical advance that makes the invention not obvious to a person skilled in the art*". Similarly section 3(d) provides that a "*mere discovery of a **new form of a known substance** which does not result in the enhancement of the known efficacy of that substance*" is not patentable under the Act. The 'Explanation' to section 3(d) provides further clarification in that "**salts, esters, ethers, polymorphs....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 therefore contended that in view of such definitions, with particular emphasis on the words "*new form of a known substance*" and "*salts, esters and other derivatives shall be considered the same substance*", the **composition** (emphasis added) comprising a compound(s) and the "pharmaceutically acceptable salts, solvates and derivatives thereof and

resolved enantiomers and purified diastereomers thereof as claimed and disclosed on page 141 of the complete specification of opposed application should not be considered an invention as they technically amount to a new form of a known substance. On the same basis, the ester protecting groups, in order to obtain the active metabolite, as claimed are also not patentable on the grounds that they should be considered to be the same substance of the already known substance, namely the unclaimed compound(s) as disclosed in the prior art disclosed in **Exhibits 8-11**, in particular **Exhibits 8 and 11**.

The Opponents further stated that section 3(d) of the Act does contain the proviso that "*salts, esters, ethers, polymorphs...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***". However, the applicant cannot rely on this proviso to claim an invention as they failed to discharge the burden of showing that the claimed composition comprising a compound(s) differs significantly in properties with respect to efficacy from other known substances other than mentioning on page 1 at lines 37-38, continued on page 2 at line 1, that "*a further object is to provide such inhibitors having elevated potency, substantial oral bioavailability (>15%) and clinically acceptable or absent toxicity compared to known compounds*". Further the specifications failed to provide any clear working examples or evidence of how any of the selected salts, hydrates and protected esters supports such a claim of bioavailability or efficacy.

The Opponent further invited the attention of Patent Office to note that bioavailability should not be equated or confused with efficacy as technically they are two separate requirements and more importantly proving efficacy requires a much higher standard. Indeed, this point was recently decided by the Chennai Patent Office in *Cipla Ltd v Novartis AG* (25 January 2006), attached as **Exhibit 4**. On page 4, paragraph 2 of that decision, the Assistant Controller clearly held that an increase of (>30%)

bioavailability between the free base and the beta-crystal form of imatinib mesylate (which was the subject matter of the patent application) did not amount to an improvement in efficacy. In light of this and the Applicant's outright failure to even attempt to demonstrate or address the question of whether the alleged invention of opposed application is significantly more efficacious than the base compound(s), they are not in a position to claim an invention.

The opponents further submitted that the compositions as claimed in the claims are not patentable under the provisions of section 3(e) of the Act, as there is no disclosure of synergy between the components of the composition within the specification and both the components are allegedly used for the same indication. Moreover, the applicant has failed to provide any enabling disclosure within the specification to prepare such a composition. As a result, the antiviral properties of the active compound(s) forming part of the composition as claimed remain as an antiviral and, therefore, the composition is simply a mere admixture resulting only in the aggregation of the properties of the compound(s).

- 10.** As regards insufficiency of description, the opponents contended that the description and claims in the specification are far too broad, ambiguous and lacking in any clarity for a skilled person in the art to be able to work the claimed invention. Not only does the specification attempt to cover a voluminous amount of compounds without any clarity, it also includes several disclaimers and variables that make the specification unclear and unworkable. For example, in relation to the changes claimed in group U₁, the specification fails to provide a problem-solution approach and adequate working explanation of why certain compounds were selected or excluded. Further, by using negative language to exclude relevant prior art the specification becomes more ambiguous about the precise nature of the invention. The purpose and importance of claims in patent applications is to define the scope of protection for a claimed invention and determine the

validity and boundaries of infringement for other inventors in the same field and therefore the applicants are required to define its invention precisely. More importantly, the claims should be able to define the invention claimed without having to rely on the descriptions or explanations given in the body of the specification.

11. The Opponent in their representation also relied upon the ground of failure of the applicants to file the application within the period of 12 months from the date of priority but have not corroborated by any evidence except the arguments that the applicants should not be allowed the multiple priorities in view of the errors in the statements given in the application form.

Submissions/arguments of the applicants:

12. 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. The applicants also submitted that the representation is based on grounds that are not available under Section 25(1) of the Patents Act, 1970, incorrect statement of facts, incorrect understanding of the patent law and inaccurate interpretation thereof and without any cogent evidence. Although the applicants have submitted their parawise reply to the allegations of the opponents denying all the grounds raised in the representation, their reply has been summarized below as per the grounds.
13. With respect to prior publication, the applicants submitted that none of the documents as cited by the opponents (**Exhibits 7-11 and 13**) anticipate the present invention and therefore irrelevant. In fact, the applicants have claimed novel compositions comprising novel compounds and the salts, solvates and derivatives and resolved enantiomers and purified diastereomers of the claimed novel compositions and compounds. The compound and compositions claimed in the present application are not a

mere derivative of known compounds as alleged by the Opponents and this has been clearly mentioned in specification (page 4; lines1-20) that they are not claiming the derivatives (i.e.) salts, solvates, resolved enantiomers and purified diastereomers) of prior art compounds. The applicants submitted the following reply in respect of each documents.

(a) Exhibit 7: It is not relevant prior art as it was published after the priority date of the present application. Moreover, it relates to novel nucleotide analogue amidates and esters, their pharmaceutically acceptable acid addition salts, a process for their production and their use whereas, the present invention relates to novel carbocyclic compounds, their novel compositions and the salts, solvates and derivatives and resolved enantiomers and purified diastereomers. **Exhibit 7** teaches that nucleotide analogue amidates are hydrolysed *in vivo* to the corresponding nucleotide analogue and are thus precursors of the corresponding nucleotide analogues whereas, compounds and compositions of present invention differ in the nature of the six-membered nucleus from the cited document which makes it a novel drug candidate and not an acid, ester or amidate. 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 is *in vivo* non-hydrolysable. Further, page 23 of **Exhibit 7** mentions that the compounds comprise any naturally occurring heterocycle found in nucleic acid, nucleotides, nucleosides or analogues. The radicals of such heterocyclic bases are the purine, pyrimidine or related heterocycles whereas, the present invention relates to carbocyclic compounds, their compositions which are orally bioavailable NAIs.

(b) Exhibit-8: The compositions of formula 1 and 1a in a passing reference include carbocyclic compounds, however, there is no preferred group or specific example of a carbocyclic NAIs found in the specification as stated by

the Opponents. Besides, the R⁵ side chain is hydrophilic in nature, whereas, the present invention has a lipophilic chain at the R⁵ 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 novel non-polar interactions are the key in achieving high binding affinity of the cyclohexene based NAI.

(c) Exhibit-9: It teaches heterocyclic and not carbocyclic compounds and therefore compositions and compounds of the present invention differ in the nature of the six membered nucleuses from the cited document.

(d) Exhibit-10: It relates to 2-deoxy-2,3-didehydro derivatives of alpha D-neuraminic acid which includes compounds belonging to the Zanamivir family which is a dihydropyran ring with the polar glycerol moiety and guanidine group as two of its side chains whereas the compounds of the present invention replace this polar glycerol moiety of these sialic acid-based inhibitors with lipophilic side chains and replace the guanidine group with the amino group. Similarly, the compounds of Exhibit-10, are slow inhibitors and can be administered only nasally and whereas the compounds of the present invention overcome the disadvantages of the cited art compound.

(e) Exhibit-11: This document discloses the rational design of two potent sialidase-based inhibitors of influenza virus replication viz. 4-amino and 4-guanidino-Neu5Ac2en as acknowledged by the applicants themselves in their brief description of related art. Both these compounds have dihydropyran ring with a guanidine or an amino group as one of its side chain whereas the present invention claims NAIs with a cyclohexene scaffold. Further, **Exhibit-11** on one hand discloses various deficiencies of these two sialidase based inhibitors and on the other hand concludes these two target compounds as the most potent influenza virus sialidase-based

inhibitors. **Exhibit-11** (Page 421, 1st paragraph lines 3-9) mentions that these sialidase based inhibitors are less active against mammalian sialidases such as human placental sialidase, bacterial sialidases and paragraph-influenza sialidase. The affinities of these compounds for human placental sialidase are about one million times lower than is observed with other sialidase based inhibitors. Further, on page 423 of **Exhibit 11** (1st paragraph lines 4-5) it is stated that 4-guanidino-Neu5Ac2en is far less effective when administered to infected mice intra-peritoneally, rather than intra-nasally.

(f) Exhibit-13: It discloses PMPA ([phosphonomethoxy)propyl]adenine) and its pro-drugs and does not teach the compounds of the present invention.

As regards priority related issues, the applicants stated that it is a matter of records that present application derives multiple priorities from US Application No. 395,245 (filed on 27 Feb 1995), US Patent No. 5,866,601 (filed on 6 June 1995) and US Patent No. 5,763,483 (filed on 29 Dec 1995). This information has been clearly provided by the Applicants in their application. The Opponent therefore with malignant intent alleged that the Applicant cannot claim multiple priority as one of the inventor is left out in the earliest priority application and that some of the claims do not reflect in one of the priority application. This allegation prima facie shows ignorance on the part of the Opponent of the Law. The applicants submitted that Section 135 and Section 137 of the Act allow multiple priorities and if those basic applications relates to constitute one invention, then a single application can be filed **by any or all of the persons** referred to as applicants in a convention country. Hence, the allegation that one of the inventors mentioned in the instant application was not mentioned in one of the three basic applications does not hold water and the opponents, without going through the provisions of the Act, has wasted the valued time of the tribunal by making a vexatious opposition. Finally the applicants submitted that the opponents have failed to prove this ground in view of the foregoing discussion.

14. While replying to obviousness, the applicants submitted that inventive step or obviousness has to be judged by a person skilled in the art. The opponents have failed to enclose any expert evidence on the matter and therefore they are not the right persons to judge the inventiveness of the present application. Further the documents filed by the opponents are irrelevant for the purpose of inventiveness. The Applicants further submitted that they have described very precisely and clearly the differences between the prior art and the present invention in pages 7 and 8 of the description given in the specification. According to the applicants, the compounds of the present invention contain lipophilic side chains whereas compounds disclosed in the prior art contain hydrophilic side chains. The compounds and compositions of the present invention are orally and intra-nasally bio-available whereas compounds of prior art are only administered intra-nasally. Besides, the present invention has a carbocyclic cyclohexene nucleus whereas the compounds of the prior art have heterocyclic oxygen pyran ring. Moreover, the compounds of prior art suffer from deficiencies like short-lived half life and unsatisfactory limitations in the manner of dosing brought on by the biological instability of the compounds. The compounds of present invention have enhanced efficacy over the known compounds and elevated potency, substantial oral bioavailability and clinically acceptable or minimal toxicity compared to known compounds. The disclosure in the prior art does not motivate to make changes in its parent compounds and arrive at the subject matter of the present invention. The applicants while replying to the ground of lack of inventive step or obviousness have also submitted same submissions in the reply as submitted for ground of prior publication.

As regards **Exhibit 5 & 6** it was submitted that these documents teach a salt selection process of a known drug candidate for drug development whereas the present invention discloses and claims compounds (and compositions) of cyclohexene scaffold which is new over the existing

heterocyclic and aromatic ring based NAIs. Hence, the Exhibits are irrelevant to the present application. They further stated that in view of such submissions and also in view of the expert evidence submitted it is clear that the subject matter of the present invention is not obvious to person skilled in the art.

15. The applicants, while replying to the ground of not an invention and not patentable, submitted that they have claimed novel compositions comprising novel compounds and the salts, solvates and derivatives and resolved enantiomers and purified diastereomers of the claimed novel compositions and compounds and not the salts and derivatives of known compounds as stated by the Opponents. The compound and compositions claimed in the present application are not a mere derivative of known compounds as alleged by the Opponents. In fact, the applicants have clearly mentioned in their specification (page 4, lines 1-20) that they are not claiming the derivatives (i.e.) salts, solvates, resolved enantiomers and purified diastereomers) of prior art compounds. Further, **Exhibit-4** (the decision of Learned Controller in *Cipla Ltd v Novartis AG dated 25 January 2006* has no relevance whatsoever to the present application. In Exhibit 4 the inhibitory and pharmacological effects of the opposed invention were the same as found in the known base compounds, only bioavailability of the claimed salt was enhanced over the known base compounds (page 3, paragraph 3, lines 4-5) whereas, the instant opposed application is claiming novel compounds, novel compositions of novel compounds and their derivatives, and not only salts or derivatives of any known compound. Also, the present invention does not teach of a mere increase in bioavailability but provides improved and less costly methods for synthesis of NAIs and provides such inhibitors having higher potency, substantial oral bioavailability 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. The claimed compounds have high oral

bioavailability and biological half-life and thus can be administered orally. Thus, cited case cannot be compared with the present application, on the ground that the applicants claim a salt, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances. Besides this, the case as cited is also *sub-judice*.

As regards the allegation that the compositions claimed in the opposed application is an admixture resulting only in the aggregation of the properties of the compounds, the applicants stated that it is completely absurd and unscientific. The fact that the composition claimed is not an admixture and has a synergistic effect is underlined by an expert of repute in his evidence

As regards not an invention, the applicants submitted that invention of the opposed application fall within the scope of the definition of 'invention' due to being novel, involve inventive step and utility. The utility of the invention has been explained in detail in pages 144-154 of the description. The compounds of the prior art suffer from numerous deficiencies like short-lived half life and biological instability of the compounds. Further, the present invention provides improved and less costly methods for synthesis of neuraminidase inhibitors and provides such inhibitors having higher potency, substantial oral bioavailability 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. It is clear from the above that the subject matter of the present invention has substantial utility in addition to the industrial applicability.

- 16.** In reply to insufficient description, the applicants submitted that the claims are clearly worded and unambiguous, a fact accepted by an expert in the art in his evidence but the opponents have invoked the various sections of the Act arbitrarily without showing the extent to how each of the section referred by them requires a proper wording of a claim and what is "proper wording".

The opponents also failed to show which part of the description is not enabled and which part of the specification is not clear. The applicants further stated that the compounds and compositions that have been claimed in the present application have been described very clearly in sufficient detail in the specification. A number of examples and schemes provided in the specification make it fully enabled and workable by a person skilled in the art. The applicants also stated that they are aware that a method of treatment is not patentable in India and accordingly have already deleted those claims. In view of this allegation of the opponents is spurious, mischievous and made with a malignant intent without proper verification. This only shows that the Opponents are bent on opposing this application without any cause.

17. In reply to the allegations that the application was not made within 12 months from the date of filing in the convention country, the applicants submitted that the instant application was filed on 26 February 1996 and in **paragraph 7** of their statement the opponents have acknowledged the fact that the present application claims priority from US application no. 395,245 filed on 27 February 1995. Therefore, the present application was filed within 12 months from the date of first named priority application in a convention country. It is evident that Opponents are trying to oppose the application just for the sake of opposing when the fact is there before them.

Consideration of grounds/submissions/arguments of both parties

18. Having given the brief about the submissions made by the opponents on each of the grounds in the representation as well as the reply thereto by the applicants, now I shall consider each of the grounds, which have been relied upon by the opponent in the light of the arguments made in the hearing, written submissions and facts of the case including their replies and evidence of the expert including the other documents submitted by both

parties. It has been observed that the opponents in their representation have relied upon the grounds namely (a) prior publication, (b) prior public knowledge or prior public use in India, (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 file convention application within 12 months but not given detail submission or any evidence in respect of prior public knowledge or prior public use in India and failure to file convention application within 12 months and therefore appears to have not pursued or contested and in view of this I am unlikely to consider them below.

However, before considering each of the grounds let me consider one issue taken up by the opponents regarding claiming of multiple priority dates based on three US applications No. 08/395,245, 08/476,946 and 08/580,567 filed on 27th February 1995, 6th June 1995 and 29th December, 1995 respectively including the one where one of inventors named in later applications but not named in earlier application. The issue is very clear as the provisions of section 137 of the Patents Act allow the applicant to claim multiple priorities based on two or more applications filed in one or more convention countries provided that application in India is made within the period of 12 months from the earliest application wherein the matter was first disclosed.

In the instant case the first US application No 08/395,245 was filed on 27th February 1995 whereas Indian patent application was filed on 26th February 1996, which means within 12 months from the date of earliest application. Secondly, under section 136(2) of the Act the applicant may also include some claims in the convention application in respect of development of or additions the invention provided they are within the single inventive concept (section 10(5)). Thirdly, the patent rules (13(6)) cast duty on the applicant to file declaration of inventorship in Form-4 alongwith the

convention application or national phase application under PCT or within such period as permitted under the said rules and permitting also to include the additional inventor. Therefore in view of the above referred provisions under the patent law, the applicants are within their right to claim multiple priorities with additional developments in the invention as well as additional name of the inventor which was not mentioned in the earliest application in convention application. However, the errors in the application form as pointed out by the opponents are typographical in nature which no way effect the interest of any person including the opponents as long as the applicants have properly disclosed the multiple applications in the application form on the basis of which multiple priorities are being claimed which have also not been disputed by the opponents. Now I will consider each ground of the opposition as relied upon by the opponents.

(a) Prior publication: For lack of novelty on the ground of prior publication, the opponents have relied upon the document namely, (a) WO95/07920 which was published on 23rd March 1995 (**Exhibit-7**), (b) WO91/16320, published on 31st October 1991 (**Exhibit-8**), (c) WO92/06691 published on 30 April 1992 (**Exhibit-9**), (d) EPO publication EP 0539204 A1 published on 28 April 1993 (**Exhibit-10**), (e) An article by Mark Von Itzstein et al, "*Rational design of potent sialidase-based inhibitors of influenza virus replication*," published in Nature, Vol.363, June, 3 1993, page 420 (**Exhibit-11**) and (f) EP 632,048 (**Exhibit-13**). I have gone through these documents and compounds of the invention disclosed in the complete specification of the application under opposition, and observed that none of the documents except WO91/16320 (**Exhibit-8**), WO92/06691 (**Exhibit-9**), and EPO publication EP 0539204 A1 (**Exhibit-10**) are relevant to constitute anticipation. It is clear from documents (WO91/16320 and WO92/06691) that the some of compounds as disclosed and claimed therein are falling within the scope of opposed application, which is the fact, applicants have

also admitted and that is the reason why the applicants have made a specific disclaimer in the claims about those compounds. This is also a fact and matter of record which has been admitted by the opponents themselves in the representation that despite some similarities, there are some differences in the features of both these inventions namely, (a) the formula I or Ia (WO91/16320(**Exhibit-8**)) covers those compounds where, **A**= oxygen, **carbon** or sulphur, and 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 the compounds of formula 1 of **exhibit-8** where A= carbon are covered within the scope of the alleged invention but the formula 1 of **exhibit-8** is capable of embracing other compounds where, A=oxygen, sulphur or nitrogen,(b) R5 side chain is hydrophilic in nature in case of D1 whereas it is lipophilic in case of instant invention, (c) The carbon is linker atom equivalent to U1 such as CH₂ whereas Oxygen, nitrogen or sulfur are linker atoms in U1 substituent of the instant invention and (d) R1 group (carboxylic in **Exhibit-8**) has been esterified in the present invention.

To invalidate the subsequent invention on the basis of prior publication, the test of anticipation was laid down 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 the information available on record, I find that there are some differences as pointed out above between the prior art documents submitted by the opponents, as well as the alleged invention disclosed in the instant application, particularly different substituents at

various positions of the carbocyclic ring structures of general formulae and accordingly the information given in the prior art documents is not equal or same to that given in the specification .Therefore I hold that the opponents have failed to prove lack of novelty on the ground of prior publication.

(b) Lack of inventiveness or inventive step: In support of this ground, the opponents have relied upon the documents namely,(a) An article by Morris, et al, *An integrated approach to the selection of optimal salt form for a new drug candidate*, International Journal of Pharmaceutics 105 (1994) pages 209-217, (**Exhibit 5**), (b) An article by Gould, *Salt Selection for basic drugs*, International Journal of Pharmaceutics, 33 (1986) pages 201-217, attached as **Exhibit 6**, (c) WO 95/07920 published on 23rd March 1995 (**Exhibit-7**), (d) WO91/16320, published on October 31, 1991 (**Exhibit-8**) (e) WO 92/06691 published on 30 April 1992 (**Exhibit-9**), (f) EPO publication EP 0539204A1 published on 28 April 1993 (**Exhibit-10**), (g) An article by Mark von Itzstein et al, “*Rational design of potent sialidase-based inhibitors of influenza virus replication*,” published in Nature, Vol. 363, 3 June 1993 page 420 (**Exhibit-11**) and (h) EP 632,048 (**Exhibit-13**) published on 4 January 1995.

During the hearing Mr.Majumdar, the agent for the opponents apart from the above documents also submitted a copy of an article by P.M.Colman, “Influenza virus neuraminidase; Structure, antibodies, and inhibitors”, published in Protein Science (1994) 3: 1687-1696 and also referred to some of the decisions of EPO Board of Appeals namely, T 0133/01, T 0355/97, and T 1212/01/97. However, Mr.Nataraj, the agent for the applicants objected to the Colman article on the ground that this document can not be submitted now as it was not referred to in the representation and also it was too late to file as same was published in 1994 and the applicants would have no time to submit the response to the same. To counter this, Mr.Majumdar submitted the copy of decision of Hon’ble High Court of Calcutta (C.O. No 407/2003) where it was held that the

plaintiff was entitled to tender the document in evidence even if same had not been presented alongwith plaint, and decision of Hon'ble High Court of Andhra Pradesh where the documents which were not filed alongwith plaint were allowed during hearing. To support his argument further Mr.Majumdar also referred the U.K. Patent Manual (Para 3.33) wherein it is stated that the hearing officer should consider the relevance of new evidence to the substantive issue. In view of the above, the article of Colman was allowed during hearing for consideration.

In T 0133/01, EPO Technical Board of Appeal held that “unsupported advantages can not be taken into consideration in respect of the determination of the problem underlying the claimed invention”. It was further held that the comparative tests have to meet certain criteria. These include the proper choice of a comparative compound to be taken from the state of art.

In T 0355/97, EPO Technical Board of Appeal held that “it is necessary in order to assess inventive step, to establish the closest state of prior art to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of claimed solution to this problem in view of the state of the art. This problem-solution approach ensures assessing inventive step on the objective basis and avoids assessing it by using an *ex post facto* analysis”. The board also held that “each of the parties to the proceedings is responsible to discharge the onus of proof about its allegations and if a party whose arguments rest on these allegations is unable to discharge the burden of proof, it loses”.

In T1212/01/97, EPO Technical Board of Appeal held that neither commercial success nor technical prejudice establishes the inventive step.

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 applicant as well as the deponent (Dr.S.Swaminathan), both have made following observations

(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(R₅) of cyclohexene ring and the balancing the lipophilicity and water solubility enhances the bio-availability of the composition whereas the compounds of prior art have R₅ side chain as hydrophilic in nature.

(d) None of the prior document teaches that if YR⁶ is not a hydroxyl group then in vivo unstable structure found at R⁵ is eliminated. The compounds of the present invention replace this polar glycerol moiety of sialic acid-based inhibitors with lipophilic side chains and replace the guanidine group of **prior** art with the amino group

(e)The cyclohexene ring of the present invention is chemically and enzymatically stable in the human GI tract.

(f) 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 the inventive step or not is to find out (a) What is 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 if the answer is negative, the invention will be non-obvious and involving the inventive step. Further, the obviousness is also a question of fact which must be decided objectively and 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 SC, 1444) while laying down certain 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 *Farbwirke 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 the 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 appear 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 submission have also admitted that prior art did

- (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) as mentioned by them in the specification **as identical** (See renumbered page No 8). In other words, the certain compounds of the prior art would have fallen within the scope of the alleged invention, had the applicants not given the disclaimer for exclusion about them in the claims.
- (c) It is also a fact on the record as well within the common knowledge of any chemist that if A is taken as carbon in the formula 1 or 1a as disclosed in WO91/16320, then what the applicants called a pyran ring, the same becomes carbocyclic ring which is same as that of the applicants.
- (d) It has also been disclosed in **exhibit-8** on page no.7 that compounds of formula (1) or (1a) can be modified at the C1 carboxyl function (at E1 of the alleged invention) to obtain the esters. Therefore

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 also obviously possible to provide further substituents at various positions of formula 1 or 1a of prior art by the person skilled in the art to obtain the compounds having desired effects.

- (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"**(Exhibit 11)**) as a relevant prior art has disclosed numerous compounds that bind neuraminidase. In fact this document confirms that the 4-amino and 4-guanidino substituted Neu5Ac2en are high affinity inhibitors for influenza virus. Therefore the substitution of guanidine group with amino group is obviously within the grasp of person skilled in the art for same purpose.
- (f) It is also clear as submitted by the agent for the opponents 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 they can be dosed orally and therefore it is not necessary to administer them by intrapulmonary or intranasal routs. This has been achieved by replacement of polar glycerol moiety of prior art compounds with lipophilic side chains and replacement of the guanidine group with the amino group in addition to replacement of Oxygen with Carbon in the ring structure.
- (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 inventive step. While evaluating the obviousness issue, above mentioned approach is 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 the technical problems underline the application.
- (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, specially 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 and opinion, I hold that the alleged invention is devoid of inventive step and obvious to the person skilled in the art.

(c) Not an invention and not patentable under section 3(d) of 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 particularly with respect to lack of inventive step or obviousness, it does not require further consideration. The contention of the opponents 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 also 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.

During hearing, Mr. Majumdar on behalf of the opponents also referred to the decisions of the controller of patents in respect of Novartis application (106/MAS/98) which was refused by the controller on the ground of section 3(d) in pre-grant opposition. Similarly, he also referred to

the judgment of Hon'ble High Court of Madras, where Hon'ble court has elaborately discussed the issues relating to section 3(d) particularly the meaning of word "efficacy" which has been defined as the ability of a drug to produce the desired therapeutic effect. To establish that the composition of the alleged invention is not efficacious than the known substance, Mr. Majumdar also submitted a document published in the journal of infection by Naoki Kawai "a comparison of effectiveness of zanamivir (known compound) and oseltamivir for treatment of influenza A and B" where the authors have concluded that zanamivir is more effective than oseltamivir for the treatment of influenza B particularly in children above 4 years and adults.

On the other hand Mr.Nataraj on behalf of the applicants refuted all the points based on these documents and submitted that they are not relevant at all. In particular Mr.Nataraj questioned the authenticity of document of Naoki Kawai, and also the study therein on various ground such as no uniformity in number of patients, maintenance of data and its authenticity. Mr.Nataraj also submitted a copy of 'Influenza Report 2006' by Kamps-Hoffmann-Preiser published by Flying Publisher wherein it is stated that Oseltamivir(one of the compounds of the instant invention) is a potent and selective inhibitor of the neuraminidase enzyme of influenza viruses A and B which can decrease the duration of influenza related symptoms if initiated within 48 hrs of onset and clinical efficacy is about 60-70% whereas the absolute bioavailability of the active metabolite from orally administered oseltamivir is 80%(pages 194-195). At the same time as per the study, Zanamivir (one of the compounds of prior art) when taken by oral inhalation, only 10-20% of the compound reaches lungs and rest is deposited in the oropharynx and approximately 4 to 17% of the inhaled dose is systematically absorbed. Zanamivir is excreted within 24 hours and serum half life after administration ranges from 2.5 to 5.1 hrs. It also has several adverse reactions (pages 214-15).

As far as the decision of the controller of patents in Novartis application is concerned it is not relevant in the present application as in that application another form (β crystalline salt) of known substance (imantib mesylate) was being claimed and this is not the case here as the present case deals with new form as other derivatives of the known compounds. Further, the said decision of the Controller is not yet conclusive due to being sub-judice at present since the matter is still pending in the Intellectual Property Appellate Board. I am also of the opinion that the judgment of Hon'ble High Court of Madras has not laid down any guidelines relating to section 3(d). Hon'ble High Court has only defined the "efficacy" in respect of pharmacological compounds besides constitutional validity of section-3(d) of the Patents Act 1970 as amended.

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 comparative data with respect to enhancement in enzymatic inhibition activities of both kinds of compounds in the specification(that means compounds of prior art viz a viz compounds of the alleged invention).I partially agree 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 particularly pyran ring compounds, the fact which the applicants have also admitted. Moreover enzymatic (neuraminidase) inhibition activities of these compounds were already identified at that time and no change in the activities was reported due to change in the ring structure. Therefore all the compounds 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 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 are in fact derivatives and have to be considered as derivatives of known compounds of formula 1a (BIOTA).

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 such 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 example 122 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 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 which was also referred 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 further mentioned that the formulations can also be prepared for sustained release. This has also been stated on page 11 (lines 30-31) of WO91/16320(BIOTA). Therefore in my opinion the alleged invention has failed to meet the requirements under these provisions in order to be patentable invention. 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.

As regards, the Influenza Report 2006 of Kamps – Hoffmann – Preiser submitted by the agent for the applicants and the article of Kawai of 2007 submitted by the agent for the opponents, both are the studies of post filing date of the instant application. Therefore, I have no option but either to consider both of them or reject both of them. On pursuing the influenza report 2006, It is observed that the said report has analysed the various factors of influenza including Avian influenza and treatment thereof including analysis of profile of various drugs such as Amantadine, **Oseltamivir** (one of the compounds of the alleged invention), **Zanamivir** (one of the compounds known in the prior art), etc. At the outset, I make it very clear that the alleged invention as disclosed in the specification is not limited to oseltamivir alone but thousands of compounds which could be derivatised from the general formula(I) and (II) and those compounds may not have the same properties as that of oseltamivir for the purpose of comparing the properties with zanamivir. Similarly the disclosure in BIOTA document is not limited to Zanamivir compound but other thousands of compounds. Therefore, it cannot be said that all the compounds of the alleged invention have same properties or oral bioavailability as that of oseltamivir and accordingly in my opinion it cannot be said that all the compounds of the alleged invention are more orally bio-available as compared to the compounds of the prior art on the basis of said Influenza Report 2006.

As far as chemical structure of oseltamivir and zanamivir is concerned, both these compounds are different in their chemical structure. However, both of these compounds are the derivative or Species of the general formula (which is Genus of these compounds) as disclosed in BIOTA application. Therefore, for the purpose of considering enhancement of

efficacy of compounds of alleged invention under section 3(d) of the Patents Act 1970 a comparison of their efficacy can be made.

It has been observed from the above mentioned report that the administration of oseltamivir, influenza symptom can be reduced within the duration of 1.5 days if taken within 36 hours of the onset of the symptoms whereas administration of zanamivir reduces the influenza symptom by upto 2.5 days if taken within 48 hours of symptoms on set. The study further states that oseltamivir treatment may be less effective for influenza B than for influenza A (for efficacy against H5 N1 strains), whereas zanamivir was shown to be efficacious in treating Avian influenza viruses H9 N2, H6 N1 and H5 N1. However said report nowhere mentioned that oseltamivir is more efficacious than zanamivir. On the contrary, the article of Naoki Kawai(2007) comparing the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B published in the Journal of Infection (2007) on the other hand concludes that there were marginally significant difference between the duration of fever after the first dose of zanamivir (31.8 ± 18.4 h) and oseltamivir (35.5 ± 23.9 h) for influenza A. The duration of fever after starting zanamivir therapy (35.8 ± 20.4 h) was significantly shorter than that of oseltamivir (52.7 ± 31.3 h) for influenza B. It also concludes that zanamivir therapy is more effective than oseltamivir for the treatment of influenza B infection. By considering the above reports, I am of the opinion that there has been no significant enhancement in the efficacy of the compounds of alleged invention as compared to the compounds of prior art and therefore falls within 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.

(d) Insufficient disclosure: In order to satisfy the requirement of sufficiency of description, the applicant for patent is under public duty 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 but not ambiguous to be understood by the ordinary skilled person.

The opponents have stated that not only does the specification attempt to cover a voluminous amount of compounds without any clarity; it also includes several disclaimers and variables that make the specification unclear and unworkable. On the other hand the applicants submitted that the claims are clearly worded and unambiguous, a fact accepted by an expert in the art in his evidence. The applicants also submitted that number of examples and schemes are provided in the specification to make it fully enabled and workable by a person skilled in the art.

On pursuing the specification, one can understand that 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. 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 of exemplary enumerated compounds 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. Accordingly I am of the opinion that the description of the invention is ambiguous and ambiguity amounts to insufficiency.

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.

19.After having considered all the circumstance of this case, representation for opposition, reply of the applicants, expert evidence in support of the applicants, 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 claimed 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 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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