

## **Skeleton Argument**

**Opposition against Indian Application No. 396/DEL/1996 A, filed on 26 February 1996 by Gilead Sciences (“the APPLICANT”)**

---

### **Skeleton Argument for Opponent**

---

1. The Opponent has learnt that on 26 February 1996, the Applicant filed for a patent titled ‘Carbocyclic Compounds’ at this Patent Office, which was allotted Application No. 396/DEL/1996 (hereinafter ‘396). ‘396 was published for opposition in the Official Journal of the Patent Office on 11 March 2005, a copy of which is attached as **Exhibit 1**. It is understood that ‘396 is currently under examination and has not as yet been granted.
2. ‘396 is an application covering ‘Carbocyclic Compounds’, otherwise more commonly known by the generic name of Oseltamivir, or the brand name Tamiflu®. The field of invention that ‘396 relates to is the area of inhibition of neuraminidase, an enzyme that is known to exist in animals and a number of microorganisms. Microorganisms containing neuraminidase are implicated to be pathogenic to man and other animals, including the influenza virus, and which can include or assist in the replication of the influenza virus through the mucus of the respiratory tract.
3. The composition comprising a compound(s) of different formulas as claimed in ‘396 derive from known antiviral compounds and compositions in the art

which act as transition-state analogue inhibitors of influenza neuraminidase, otherwise called neuraminidase inhibitors (NAI). However, the Applicant claims the composition comprising a compound(s) as claimed within '396 provides an improvement over other such known compounds and compositions for the inhibition of neuraminidase. In particular, the Applicant claims in '396, on page 1 at lines 30-38 and on page 2 at lines 1-5, that the invention overcomes numerous deficiencies existing in compounds of the art including, ephemeral biological half-life and unsatisfactory limitations in the manner of dosing brought on by the biological instability of the existing compounds.

More specifically, the Applicant's claims within '396 may be summarised as follows:

- a) Claims 1-37 and 40-71 claim a composition comprising a compound of formula (I) or (II) and the dependant claims. Claim 71 is an omnibus claim.
- b) Claims 38, 39 and 72 provide a method for inhibiting the activity of neuraminidase, wherein claim 72 is an omnibus claim.
- c) Claims 69 and 70 provide for use of a compound for preparation of another compound.

d) Claim 73 claims a process for preparing a composition comprising a compound as claimed in claim 1 and also includes an omnibus claim.

4. The Opponent has closely studied the specification and claims made by the Applicant in '396 and strongly believes that the invention is not patentable under the following grounds of s25(1) of the Act:

a) s25(1)(b)(ii) - that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim elsewhere in any other document.

b) s25(1)(e) – that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.

c) s25(1)(f) – that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under sections 3(d) and 3(e).

d) s25(1)(g) – that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

- e) s25(1)(i) – that in the case of a convention application, the application was not made within twelve months from the date of the first publication for the invention made in the convention country by the applicant or a person from whom he derives title.

Accordingly, as permitted under s25(1) of the Act, which allows an opposition to be filed by any person after publication but before the grant of a patent, and Rule 55(1) of the Rules, the Opponent submits its opposition to ‘396 on the grounds set out below. Furthermore, as ‘396 was filed at this Patent Office (New Delhi), the Patent Controller of the said office has the jurisdiction to hear and decide on this opposition

### **GROUND**

The Opponent submits its opposition on the following grounds:

**Claims 1-37, 40; 41-68 and 71 of the invention are not patentable under sections 2(1)(j), 2(1)(ja), s3(d), s3(e), 25(1)(e) and (f) of the Act.**

5. The alleged invention in ‘396 is not patentable under sections 2(1)(j), 2(1)(j(a), 3(d) and 3(e), as the wording of the preamble of the claims, when construed literally, can only be interpreted as claiming a composition comprising a compound of two formulas and not the actual carbocyclic compound(s). As a result, the actual composition claimed in ‘396 is not capable of claiming novelty or an inventive step.

6. The Applicant in its main independent claim, claim 1, and all dependant claims, has chosen to use the words “composition comprising a compound” as the preamble for each claim and the qualifying substitutions, rather than adopt the much clearer language and standard practice of “A compound of formula (I) or (II)” or “A compound of claim 1 wherein”. By adopting such phraseology, the Applicant is deliberately being ambiguous, imprecise and misleading. Indeed, this trend of ambiguity and lack of clarity in the claims for ‘396 is also prevalent within the descriptions provided in the specification. The Opponent strongly believes that this Patent Office should construe the words “composition comprising a compound” literally for the sake of certainty, so as not to allow the Applicant the option to determine or broaden what the claims are supposed to mean at a later stage of the application process. By applying such a literal interpretation to the claims in ‘396, the Applicant is, therefore, merely claiming a composition comprising a compound(s) and not the actual compound(s).

7. Reading the above literal construction of the claims in the light of sections 2(1)(j), 2(1)(ja) and s3(d), the claimed invention in ‘396 is not patentable. s2(1)(j) clearly provides that an invention means “*a new product involving an inventive step*”, while s2(ja) defines 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*”. Section 3(d) helps to clarify sections 2(1)(j) and (ja) by holding 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 considered an invention and is not patentable under the

Act. The 'Explanation' to s3(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*".

In view of these 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 in claims 1, 9, 10, 12-15 or as disclosed on page 141 of '396 should be considered as being the same substance. as known substance. On the same basis, the ester protecting groups, in order to obtain the active metabolite, as claimed in claim 32 of '396 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 base compound, Oseltamivir.

8. The Opponent recognises, however, that s3(d) 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 Opponent contends that the Applicant cannot rely on this proviso to claim an invention for '396, as '396 fails to even attempt to discharge, let alone discharge, its 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 in passing on page 1 of '396 at lines 37-8, 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*", '396 fails to provide any clear working examples or evidence of how any of the selected salts, hydrates and protected esters support such a claim of bioavailability or efficacy.

The Opponent would like the Patent Office to note that the Assistant Controller of the Chennai Patent Office in the matter concerning Application No. 1602/MAS/98 by Novartis AG, attached herein as **Exhibit 2**, 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 '396 is significantly more bioavailable or efficacious than the base compound(s), the Applicant is not in a position to claim an invention.

9. In addition to the above, the claimed composition comprising a compound(s) and the "pharmaceutically acceptable salts, solvates and derivatives thereof and resolved enantiomers and purified diastereomers thereof" and protected esters are devoid of any novelty and/or inventive step. It is well known in the field of pharmacology that pharmaceutically acceptable salts such as the alkali, alkali earth salts, organic and inorganic acid addition salts as claimed

in '396, and described on page 141, do not amount to being novel and/or having any inventive step.

10. It has long been common knowledge in the pharmaceutical industry that the conversion of a lead molecule into a pharmaceutically acceptable salt can result in numerous advantages, including improved dissolution rate and bioavailability. Various prior art exists which provide clear directions to finding the optimal salt for any given new drug candidate in order to improve the overall properties of a drug. For example, 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, attached as **Exhibit 3**, 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. The Opponent also refers to the article by Gould, *Salt Selection for basic drugs*, International Journal of Pharmaceutics, 33 (1986) pages 201-217, attached as **Exhibit 4**, which also substantiates the above points and lists the commonly used commercial salts. Therefore, the Opponent contends that the salt selection claimed by the Applicant in '396 in order to 'improve' the basic molecule

does not amount to novelty and/or an inventive step and accordingly should be rejected.

11. The above contention also applies to claim 32 of '396 with respect to the active acids, protected esters and amides in order to attain the active metabolite of the basic compound(s). Aside from the fact that the active metabolite would be inherently anticipated from the known antiviral nature of the compound(s) within '396 anyway, and is therefore lacking in any novelty and/or inventive step, the prior art of WO 95/07920 (hereinafter '920) which was published on 23 March 1995, attached as **Exhibit 5**, on page 23 at lines 10-30 of the specification already discloses the esters of the active acids claimed by the Applicant. The Applicant has obviously adopted, without any improvement or invention, the approach disclosed in the prior art to claim the active acids, protected esters and amides in '396. The Opponent wishes to highlight that '920 is relevant prior art given that the Applicant only provided an enabling disclosure for the active acids, protected esters and amides in claim 32 in the claimed priority application '483 which dates from 29 December 1995.

12. In the alternative and without prejudice to the above, the compositions claimed within '396 are not patentable in light of s3(e), 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 '396 to prepare such a composition. As a result, the

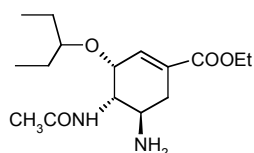
antiviral properties of the active compound(s) forming part of the composition claimed remain as an antiviral and, therefore, the composition does not qualify as an invention but is simply a case of a mere admixture resulting only in the aggregation of the properties of the unclaimed compound(s).

**Claims 1-37, 40; 41-68 and 71 of the invention are not patentable under sections 2(1)(j), 2(1)(ja), 25(1)(b)(ii), 25(1)(d), 25(1)(e), 25(1)(f) and 3(d) of the Act**

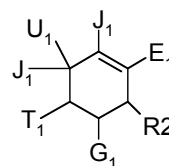
13. Without prejudice to the arguments set out by the Opponent in paragraphs above, even if the claims made in '396 can be construed to cover the basic compound(s), the claimed compound(s) have already been disclosed or amount to derivatives from the earlier compounds and compositions published elsewhere as prior art. The Opponent relies on the prior art WO 91/16320 (hereinafter '320), which was published on 31 October 1991, attached as **Exhibit 6**, WO 92/06691 (hereinafter '691) which was published on 30 April 1992, attached as **Exhibit 7**, EP 0539204 A1 (hereinafter '204) which was published on 28 April 1993, attached as **Exhibit 8**, and an article by 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"), attached as **Exhibit 9**, as the relevant prior art which disclose numerous compounds that bind neuraminidase and have a nucleus as claimed in '396. The Applicant has referred to the above relevant prior art in

'396 on page 2 but has cleverly used negative language on page 7 at line 10 and throughout the claims, such as claims 2 and 9, to exclude the same. While the Applicant may argue that this amounts to a disclaimer of the prior art from the claims made in '396, 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.

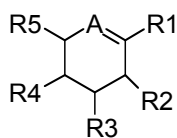
14. Claim 1 of 396 may be represented as set out below, wherein the various functional groups are broadly represented as  $E_1 = \text{COOEt}$ ,  $J_1 = \text{H}$ ,  $G_1 = \text{NH}_2$ ,  $U_1 = \text{O}(\text{CH}(\text{C}_2\text{H}_5)_2)$  and  $T_1 = \text{NHCOCH}_3$ . When substituted by the functions covered in claim 1, the structure represents the compound structure for Oseltamivir as shown below.



or



Of the prior art noted above, '320 (**Exhibit 6**) and the Von Itzstein article (**Exhibit 9**) are the most relevant and which negate any novelty claimed for the compound(s) in '396. Formula I(a) of claim 1 in '320 is represented as set out below, wherein the various functional groups may be represented as  $A = \text{C}$ ,  $R_1 = \text{COOC}_2\text{H}_5$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{NH}_2$  and  $R_4 = \text{NHCOCH}_3$ .



If one replaces the groups A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> by the functions claimed, it reveals a structure that has very little difference to that claimed in '396. The only difference between the structures claimed in '320 and '396 resides in the group U<sub>1</sub> of '396, whereas U<sub>1</sub> forms a C-O linkage with the ring whilst the corresponding R<sub>5</sub> of '320 forms a C-C linkage with the ring. Indeed, this is clearly admitted by the Applicant in '396 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 '396 with the compounds claimed in '320. Technically speaking, the class of compounds claimed in '396 were simply selected, or more accurately derive from the art, in particular '320, and as a result should not be considered novel.

15. In the alternative and without prejudice to the above, even if the invention claimed in '396 is considered novel over the prior art, the Opponent believes that it does not meet the requirements of sections 2(1)(j) and 2(1)(ja) as it lacks any inventive step and technical advance. Page 7 at line 28 onwards of '396, as discussed in paragraph 19 above, discloses clearly the lack of inventive step and obvious nature of the steps taken for the claimed invention. The Applicant's disclaimer on page 7 at line 15 that the compositions and compounds claimed in '396 exclude compounds that are obvious under s103 of the United States Code Title 35 – Appendix L Patent Law (35 USC),

attached herein as **Exhibit 10**, has no bearing on how '396 should be examined by this Patent Office.

As can be seen, the standard of obviousness set out under 35 USC 103 is more liberal and has a lower standard than that required under the Indian Act. In particular, 35 USC 103 requires that the "*subject matter as a whole would have been obvious*" and that "*patentability will not be negated by the manner in which the invention was made*". Moreover, to obtain the full picture, 35 USC 103 should be read with 35 USC 100 and 101 (see **Exhibit 10**) which explicitly makes no differentiation between an invention and a discovery and also grants patents for 'useful improvements', which is all too often interpreted liberally in the U.S and which obviously does not meet the high standards of patentability and efficacy set in s3(d) as discussed below. In view of the above, it is submitted that this Patent Office should not be swayed by the standards of obviousness adopted by one of the most patent friendly jurisdictions in the world.

16. The slight modifications made in '396 over the prior art as attached in **Exhibits 6-9**, in particular '320 (**Exhibit 6**) and the article attached as **Exhibit 9**, 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 -CH<sub>2</sub>- moiety, which is the only minor difference between '396 and the

prior disclosed art, the Applicant could still expect similar properties from the parent compounds of the prior art disclosed in **Exhibits 6-9** and its ring equivalents as claimed in '396 at claim 2.

17. In support of the above, the Opponent contends that the minor modification in group U<sub>1</sub> of '396 by the Applicant was pre-conceived and obvious in order to prepare a carbocycle 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 recognise that to achieve this outcome one of the first steps would be the replacement of the oxygen of the pyran ring by a -CH<sub>2</sub> - moiety or prepare a carbocycle. Indeed, page 3 at lines 20-26 of '320 effectively discloses the formula for obtaining a carbocyclic of neuraminidase inhibitor as claimed in '396 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 strongly believes that the steps claimed by the Applicant in '396 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 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  $-CH_2-$  replacement to achieve the desired effect

18. In addition and related to the above, '396 implicitly claims the prodrug of Oseltamivir by claiming "pharmaceutically acceptable salts, solvates and derivatives thereof and resolved enantiomers and purified diastereomers thereof" of the compounds claimed and the active acids esters and amides to obtain the active metabolite. With respect to the claiming of the pharmaceutically acceptable salts, the Opponent argues that such claims do not amount to an inventive step and are obvious in light of the arguments stated in paragraphs above.

19. As admitted by the Applicant on page 24 at line 1 and throughout page 25 of '396, 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 (hereinafter '048) which was published on 4 January 1995, attached as **Exhibit 11**, and '920 (see **Exhibit 5**). Therefore, in light of the earlier prior art, the Applicant's claim for pharmaceutically acceptable salts and active acid esters to improve the bioavailability of the

claimed invention in '396 is not only anticipated but does not add any inventive step. Moreover, and as discussed above already, the Applicant has 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.

20. As for the Applicant's claim for the active metabolite for the compound(s) of the invention, as claimed in claim 15 and disclosed in Scheme 28 and Example 94 of '396, there can be no inventive step here and the Opponent repeats its arguments set out above. The Applicant would have known about the NAI properties of the claimed compound(s) from the prior art discussed above and, therefore, would have been inherently anticipated. In fact, any claim for the obtaining of the active metabolite is anticipated and/or made obvious from the disclosure in the prior art '920 and '048 which describes the acids as metabolites of the respective esters and which have obviously been incorporated into '396 by the Applicant, as explained on page 25 at line 30 of '396.

21. In the alternative and without prejudice to all the above, the arguments put forward by the Opponent are entirely supported by the wording of Section 3(d) of the Act. As highlighted in the paragraphs above, namely 13, 14 15 and 16 the compound(s), pharmaceutically acceptable salts etc and active metabolite claimed within '396 are not patentable under s3(d) as they are to be considered as derivatives of a known substance. In this case, as '396 obviously derives from the prior art disclosed in **Exhibits 6-9**, in particular **Exhibits 6** and **9**, and salts esters, active metabolites of a known substance shall be considered to be the same substance, the invention claimed by the

Applicant is clearly not patentable. Even though Section 3(d) of the Act does include the exception that the derivatives of known substances that can show that they differ significantly in properties with regard to efficacy are patentable, the Applicant has failed to even attempt to discharge, let alone overcome the hurdle set by Section 3(d). As already mentioned above, the most the Applicant can muster to meet the requirements of s3(d) is to make a general claim that the compound(s) claimed in '396 are orally bio-available. For this Patent Office to accept such a broad, sweeping statement from the Applicant as meeting the high burden of patentability set by s3(d), would be to ignore s3(d) entirely and the purpose for which it was included in the Act. The Opponent therefore repeats the arguments set forth above.

**Claims 1-37, 40; 41-68 and 71 of the invention are not patentable under the sections 10(4)(a) and (b) and 25(1)(g) of the Act.**

22. In the alternative and without prejudice to all the above, the Opponent contends that the specification and claims for '396 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 by the Applicant in group U<sub>1</sub>, the specification fails to provide a problem-solution approach and adequate working explanation of why certain compounds were selected or excluded. The Opponent is firmly of the view that the specification and claims as drafted is a deliberate attempt by the Applicant to camouflage the

claims made in '396 from being anticipated by the prior art discussed above and the obviousness of the invention.

**Claims 38, 39, 69, 70, 72 and 73 of the invention are not patentable under sections 2(1)(j), 2(1)(ja), 25(1)(b)(ii), 25(1)(d), 25(1)(e), 25(1)(f) and 25(1)(g) of the Act.**

23. The above claims should be rejected on the grounds that the methods of preparation described and claimed are for inhibiting the activity of neuraminidase for compound(s) that are not novel and/or obvious and, therefore, are matters of normal design procedure that would be commonly known to the skilled man. It should be noted that an analogous process for the preparation of compound(s) is only acceptable in connection with a patentable product. Furthermore, the omnibus claims of claim 72 and 73 should be refused under s25(1)(g) as they fail to provide any clarification to a specification that already fails to provide the best method for working the claimed invention. As result, they serve little purpose and should be refused.

Based on the grounds set out in paragraphs above, the Opponent requests that Application No. 396/DEL/1996 be refused in its entirety and without the opportunity for an amendment to the claims made therein. As permitted under Section 25(1) of the Act and Rule 55(1) of the Rules, the Opponent requests that this Patent Office informs the Opponent immediately of any response filed by the Applicant to this opposition and also grant the Opponent a hearing in the above matter.

Dated    day of    2006

For and behalf of \_\_\_\_\_

\_\_\_\_\_

Our address for service in connection with these proceedings is:-

\_\_\_\_\_

To:

The Controller of Patents

The Patent Office, NEW DELHI