THE PATENTS ACT, 1970

In the matter of an Application for Patent
No. IN/PCT/2002/1536
AND
In the matter of pre-grant opposition to the grant
Of a Patent thereon under Section 25(1)
AND
In the matter of Section 15

OTSUKA PHARMACEUTICAL CO. LTD ..... Applicant

TORRENT PHARMACEUTICALS LIMITED Opponent

Present:
1. DR.S.BANERJEE ..... For The Applicant

2. MR.S.MAJUMDAR AND DR.S.GANGULI ..... For the Opponent

Hearing held on 12/07/2017.

Brief History of the Application:

1. An application for patent IN/PCT/2002/1536 was filed on 17/12/2002 by OTSUKA PHARMACEUTICAL CO. LTD OF JAPAN for their invention entitled "HYDRATE A OF ARIPIPRAZOLE AND A PROCESS OF PREPARATION THEREOF" through their Agent L.S.davar & Co., Kolkata which was a national phase application of the PCT international application number PCT/JP02/09858 dated 25/09/2002 and claimed priority from two Japanese and one Canadian applications and priority application numbers are 2001-290645, 2001-348276 and 2379005, dated 25/09/2001, 14/11/2001 and 27/03/2002 respectively.

2. This application was examined in accordance with the provision of the Patents Act 1970 (as amended) and First Examination Report (herein after called as FER) was issued to the Applicant's Agent on 01/08/2005.

3. A pre grant opposition u/s 25(1) of The Patent Act, 1970 was filed by TORRENT PHARMACEUTICALS LIMITED OF GUJRAT against application no. IN/PCT/2002/1536 filed by OTSUKA PHARMACEUTICALS CO. LTD with the following grounds:

a. that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim (i) In any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or (ii) In India or elsewhere, in any other document.
b. that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;
c. that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim;
d. that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (a) or having regard to what was used in India before the priority date of the applicant's claim;
e. 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;
f. that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;
g. the applicant has failed to disclose to the Controller the information required-by Section 8 or has furnished the information which in any material particular was false to his knowledge.

The Opponents also submitted Exhibits as evidences, namely the exhibits are

1. EP0367141
2. DSC values of Example 1 of Exhibit 1.
3. US4734416
4. Satoshi Aoki et al "Study of transformation of aripiprazole Proceeding of the 4th Japan -Korea symposium on separation technology, Tokyo October 6-8 1996".
5. EXHIBIT 3A- Enlarged Figure 3c of Exhibit 3.
6. EXHIBIT 3B- Enlarged Figure 3a of Exhibit 3
7. EXHIBIT 3C- Experimental evidence and 26 values of Example 1 of Exhibit 1.
8. EXHIBIT 4- Yasuo Oshiro Et al "Novel antipsychotic agents with dopamine autoreceptor agonist properties: synthesis and pharmacology of 7[4-(4 phenyl -1- piperazinyl) butoxy] -3,4-dihydro- 2(lH)- quinolinone derivatives." Journal of Medical Chemistry, American Chemical Society Washington US Vol 41 no 5, 26th February 1998,
9. EXHIBIT 5- CDER Memorandum.

Opponent also submitted Evidence in Reply from Ramesh Chandra Gupta.

4. In reply to opponent's written statement and evidences, the applicant under the provisions of Patents rules 55(4) also filed the reply statement on 06/04/2010 along with Original notarized and stamped Affidavit and amended claims.

5. After completion of the procedure prescribed under section 25(1) to read with Rule 55 under prevailing Rules a Hearing was fixed on 12/07/2017 at 11.30a.m to dispose the pre-grant opposition.

6. The hearing was held as per schedule. The Agent of the Applicant and Agent of the Opponent were present on date of hearing. After completion of the hearing the applicant and also opponent were directed to file written note of arguments and the Agent of the opponent submitted the same within the statutory period. But the Applicant submitted a request along-with petition for extension of time for filing their written submission. The same has been taken care of and the applicant submitted the same on 23/08/2017.

7. At time of hearing the Agent of the opponent relied on following grounds and grounds are lacking in inventive step and section 3(d).
8. Other grounds namely prior claiming and Section 8 were dropped at the time of hearing and the Opponent also submitted that for the other grounds the submissions on record to be considered.
9. Upon consideration of the grounds of opposition raised by opponent *vis-a-vis* the arguments placed by the applicant under the provision of section 25(1) of the Act and prevailing Rules followed by written note of argument by the applicant, I shall turn my eyes to the grounds of opposition, on record as submitted by the opponent for pre-grant opposition and subsequent submission thereby from the applicant and discuss some of the pertinent grounds in my consideration.
10. The opponent argued on lacking in inventive step at time of hearing. So first I consider the ground of lacking inventive step. While arguing obviousness the opponent relied on following documents: Exhibit 1 (EP 0367141), Exhibit 2 (US4734416), Exhibit 3(Satoshi Aoki et al "Study of transformation of aripiprazole Proceeding of the 4th Japan -Korea symposium on separation technology, Tokyo October 6-8 1996"), Exhibit 4 (Yasuo Oshiro Et al "Novel antipsychotic agents with dopamine autoreceptor agonist properties: synthesis and pharmacology of 7[4-(4 phenyl -1- piperazinyl) butoxy] -3,4-dihydro- 2(lH)- quinolinone derivatives." Journal of Medical Chemistry, American Chemical Society

Washington US Vol 41 no 5, 26th February 1998) and Exhibit 5 (CDER Memorandum).

11. The opponent argued that the applicant has not denied or disputed the ground of inventive step in their reply statement and the applicant only submitted their view regarding novelty but silent about inventive step. Then the opponent submitted: "The Opponent submitted that the Applicant refers to paragraph 6 which pertains to novelty so it is not clear why the Applicant has mentioned that the impugned invention possesses inventive step; further since no arguments have been made for inventive step. In the following pages of the Reply Statement, the Applicant allegedly goes on to show that the Hydrate A is novel and not disclosed in any of the Exhibits. The Opponent respectfully submits that the Representation mentions that Satoshi Aoki et al "Study of transformation of aripiprazole Proceeding of the 4th Japan —Korea symposium on separation technology, Tokyo October 6-8 1996" (Exhibit 3) discloses hydrate A of the impugned invention. The powder X-ray diffraction spectrum of the Hydrate A of the impugned invention is shown in Figure 3. However, when the powder X-ray diffraction spectrum of known Hydrate Type 3 (Enlarged Fig. 3c of Exhibit 3 as annexed as Exhibit 3A) is compared (taking into account the difference in scale) with the powder X-ray diffraction spectrum of Figure 3 of the impugned application, a perfect match is found (within a reasonable tolerance and taking into account the small size of Fig. 3c), thus indicating that the two polymorphs are identical, and therefore that the Hydrate A is not novel, as it was available to the public before the priority date of the impugned application."

12. Further the opponent submitted: "Further, the Opponent submitted that as admitted in the specification at page 35 the Type C to F crystals of aripiprazole anhydride of the present invention correspond to the Type-III to VI crystals of aripiprazole anhydride disclosed in JP-2001-348276. The Opponent further submitted that the process of preparation of anhydride B crystals of the impugned invention involves heating Hydrate A at 90-125°C for 3-50 hours. Exhibit 3 also discloses that Type III (Hydrate B) is heated at 80°C to yield anhydride Type I. The Opponent submitted that there is nothing inventive in only slightly modifying the temperature of the process. A change in prior art temperature from 80°C to 90-125°C of the impugned invention is mere

optimisation of temperature. This is routine experimentation for a person skilled in the art to optimise parameters of a process. The Opponent pointed out that the Applicant has acknowledged in the Reply Statement on page 13 that the impugned invention is directed to novel crystalline polymorphs and hydrate of aripiprazole which is clearly distinguishable from the known aripiprazole. It was submitted by the Opponents that on page 13, after discussing the novelty of the invention the Applicant refers to paragraph 8.1 of the Representation which pertains to prior public use and public knowledge. It was reiterated that inventive step has not been discussed in the Reply Statement. The Applicant then moved to Paragraphs 9.2 and 9.3 which pertains to Section 2(1)(l) and 3(d), respectively but completely omits any discussion on paragraph 9.1 which pertains to section 2(1)(ja), again not categorically disputing the lack of inventive step of the impugned invention. Section 2(1)(l) relates to new invention and again the Applicant has only justified the novelty of the impugned invention. The Evidence submitted along with the Reply Statement also do not make any arguments for establishing inventive step. The Opponent asserted that since the Applicant has not disputed lack of inventive step or even denied lack of inventive step, it goes on to show that the Applicant has accepted lack of inventive step of the invention. The Applicant has only justified the novelty of the impugned invention. However, the Opponent respectfully requested the Ld. Controller to decide on the novelty of the impugned invention. The Opponent respectfully submitted that detailed submissions for lack of inventive step are already recorded in the Representation and are not repeated at the time of the hearing. Furthermore, a lack of inventive step is established since there is no rebuttal from the Applicant in the Reply Statement."

13. Then the opponent submitted their view regarding section 3(d). In the submission the Opponent submitted: "The Opponent submitted that the Applicant has also substantially failed to dispute the ground of Section 3(d). With reference to paragraph 9.3, the Applicant states in the Reply Statement that the invention is novel and inventive and therefore patentable. The conclusion of patentability of the invention has only been based on the novelty and the inventive step. 9 Without prejudice that the invention lacks novelty and inventive step, the Opponent submits that the validity of the impugned invention is also

questionable as the invention falls within he mischief of Section 3(d). The Applicant has made no projection towards an effect that the invention is outside Section 3(d). In the Reply Statement the Applicant has stated that as the Indian Patent Law stipulates that crystal polymorphs which cannot be necessarily produced by a preparing method as prior art and having clearly different effects are allowable. The Opponent submitted that a method which is disclosed in the prior art is different from a method which can be derived from common general knowledge. The Opponent further submitted that the crystal polymorphs are made by methods which are derived from common general knowledge. Further, the Applicant has not shown any different effects exhibited by the polymorphs of the impugned invention. The fact that the Applicant itself refers to the aripiprazole forms of the impugned invention as crystal polymorphs attracts section 3(d). The burden of proof to show that the polymorphs of aripiprazole does not fall within Section 3(d) is on the Applicant. However, the Applicant has failed to dispose of the burden as the Applicant has failed to show any enhanced therapeutic efficacy of the forms of aripiprazole of the impugned invention. The Applicant has mentioned in the Reply Statement that the polymorphs and hydrates of aripiprazole has reduced hygroscopicity, better solubility, more bioavailability, and improved shelf life which renders them superior to the prior art compounds. However, there is no data on efficacy, particularly therapeutic efficacy, which is a requirement of Section 3(d)."

14. The opponent also submitted order of the Hon'ble Supreme Court in Novartis vs. Union of India & Others.

15. Further the opponent submitted: "The Opponent further asserted that an objection on Section 3(d) was also raised in the Further Office action issued by the Patent Office. However, there also the Applicant failed to address the objection and combined the response with the objection on novelty. There to the Applicant argued for the establishment of the novelty of the aripiprazole forms of the impugned invention. The opponent submits that to come under the purview of Section 3(d), a compound has to be a new form thus it is necessary for the compound to be novel. The Applicant has admitted multiple times that the polymorphs are new and also that they are new forms of already known aripiprazole. Therefore, the polymorphic forms will attract Section 3(d). The

Opponent stated that if the forms of the aripiprazole are not new forms then they are not novel and lacks novelty. So if the Applicant states that the forms are novel then they are new forms and fall under Section 3(d) and if these are not new forms, then they lack novelty."

16. Now I consider the counter argument of the applicant submitted after hearing. In written submission the applicant submitted that none of the cited documents of opponent discloses about Aripiprazole hydrate A or anhydrous aripiprazole crystals B to G. Further the applicant submitted: "Finding Aripiprazole Hydrate A and using it have achieved to industrially and stably obtain anhydrous aripiprazole crystals B for a pharmaceutical solid oral preparation such as a tablet, flashmelt, etc. To be able to industrially and stably obtain the novel Anhydrous Aripiprazole Crystal B indicates that it is possible to stably provide a drug being useful for a society. This is very important for the pharmaceutical industry. Such the technology had been achieved by the present invention by finding of the Aripiprazole Hydrate A. This is not disclosed nor suggested in Exhibit 1 to 4 cited by the opponents. Therefore, it would have not been easily conceivable for one skilled in the art referring to Exhibits I to 4 cited by the opponents to achieve the present invention. Further, conventional aripiprazole hydrate (type 3 of Exhibit 3 cited by the opponents) is disclosed on page 63, Reference Example 3 of the original English specification of the present application. The data of the termogravimetric/differential thermal analysis are depicted in Figure 6 and the data of X-ray diffraction spectrum are depicted in Figure 7. Aripiprazole Hydrate A of the present application is disclosed in page 6T, Example 1 of the original English specification of the present application. The data of the termogravimetric/differential thermal analysis are depicted in Figure 1 and X-ray diffraction spectrums are depicted in Figure 3."

17. Then the applicant submitted: "As mentioned above, conventional aripiprazole hydrate (type of Exhibit 3 cited by the opponents) and Aripiprazole Hydrate A are clearly different. Exhibit 1, 3 and 4 cited by the opponents describe aripiprazole but they do not clearly disclose anhydrous aripiprazole crystals B having low hygroscipicity of the invention of the present application. Exhibit 3 cited by the opponents does not disclose specific aripiprazole per se. In addition, it does not clearly disclose anhydrous aripiprazole crystals B having low hygroscopicity of the

inventions of the present application. The present invention for the first time had enabled one to obtain Aripiprazole having low hygroscopicity which does not tend to be a hydrate form (this aripiprazole does not decrease its dissolution rate after long time storage. Namely, it can maintain a maximum drug concentration Cmax.)."

18. Further the applicant submitted: "Especially, as comparing the thermogravimetric/differential thermogram between Fig.1 (Aripiprazole Hydrate A of the present application) and Fig. 6 (type 3 crystals of "The 4th Japanese-Korean Symposium on Separation Technology (October 6 to 8 1996)-, the endothermic curve is quite a different from each other. That is, Fig. 6 has a characteristic sharp peak around 123.5oc, while Fig. 1 does not have such a peak around 123.5.c. Thus, aripiprazole hydrate A of the present application is clearly different from the conventional hydrate of aripiprazole. Of course, any prior art reference neither discloses nor suggests the process for preparing the hydrate A.

Accordingly, aripiprazole hydrate A of the present application has inventive step in view of any prior art references. In conclusion, the present invention is directed to forms of aripiprazole and hydrate of aripiprazole, being clearly distinguishable from the known aripiprazole. Thus, the aripiprazole hydrate A of the present invention has reduced hygroscopicity, better solubility, more bioavailability and improved shelf life. [n view of the above submissions, the aripiprazole hydrate A of the present invention do not lack inventive step in view of the documents cited by the Opponents."

19. Further the Applicant submitted the crystals are hygroscopic in nature, so they stick to manufacturing instrument and this is a loss for manufacturing process. Then the applicant argued that there is a large number of process claim which are well supported by the description and also submitted: "Thus, the applicants disagree that the process of preparation of aripiprazole hydrate A and anhydrous crystals B is routine experimentation and any person skilled in the art would be able to perform all the process along with the proper process parameters and steps as taught in the specification of the present invention. Further, all the documents cited by the Opponents fails to teach such process of the present invention. In other words, none of the cited document teaches of the process disclosed in the instant specification. In the specification it is clearly mentioned

that each of the aripiprazole forms of the present invention has reduced hygroscopicity, better solubility, more bioavailability and improved shelf life. Thus, such properties of the product of the present invention renders the compounds more superior to the prior art compounds. The applicants disagree to the opponents' allegation that the specification has insufficient disclosure. The specification gives a complete disclosure of the present compound, process for preparation and their efficacy with respect to the experimental data. The examples are also given in support of the description. The opponents allege that dissolution property and bioavailability are not sufficiently disclosed. However, Table I on page 85 of the specification as originally filed describes that the anpiprazole forms of the present invention are superior in the dissolution property to that of aripiprazole of prior art. Further, the aripiprazole forms of the present invention are superior in the bioavailability to that of aripiprazole of prior art. As mentioned above, this is disclosed as the dissolution test in Table 2 on page 98 and Table 5 of page 99 of the specification as originally filed. Therefore, they are originally sufficiently disclosed in the specification on the filing date."

20. Lastly the applicant submitted: "With these submissions, we request the Ld. Controller to at least allow the process claims which are well supported by the description and examples as pointed during the Hearing as well as in our Written Submissions."

DECISION:

21. It is to be noted that at time of hearing , the Opponent narrow down the grounds of opposition and these grounds were already present at time of filing the opposition. The main grounds are: lacking in inventive step and section 3(d).

GROUND INVENTIVE STEP:

22. After going the submissions/arguments of both Opponent and Applicant, now I would like to consider the issues accordingly. First I consider objection regarding inventive step. For inventive step, I go through the cited documents as given by the opponent.

Cited document EP0367141 discloses about novel carbostyril derivatives and process of preparation thereof. I go through the example 1. Example 1 describes about aripiprazole and its various type of salts and their preparation. Here I reproduce the example 1 and it reads as "A suspension of 47 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, 35 g of sodium iodide with 600 ml of acetonitrile was refluxed for 30 minutes. To this suspension was added 40 g of 1-(2,3-dichlorophenyl)piperazine and 33 ml of triethylamine and the whole mixture

was further refluxed for 3 hours. After the solvent was removed by evaporation, the residue thus obtained was dissolved in chloroform, washed with water then dried with anhydrous magnesium sulfate. The solvent was removed by evaporation, and the residue thus obtianed was recrystallized from ethanol twice, to yield 57.1 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.
Colorless flake crystals
Melting point: 139.0 -139.5°C.

One gram of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril was dissolved in 20 ml of ethanol by heating, then under stirring condition, an ethanol solution saturated with hydrogen chloride was added thereto, the crystals precipitated were collected by filtration and recrystallized from thanol to yield 0.75 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril hydrochloride.
White powdery substance
Melting point: 214-222°C. (decomposed).

One gram of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril was dissolved in 10 ml of ethanol, then to this solution was added 4 ml of sulfuric acid-ethanol (1ml of concentrated sulfuric acid/10 ml of ethanol), then the solvent was removed by evaporation. To the residue thus obtained was added 10 ml of ethanol and 30 ml of water, the mixture was heated to make it as a solution, recrystallized, and the crystals were collected by filtration, further recrystallized from ethanol-water to yield 1.02 g of 7-{4-[4-(2,3-dichloro phenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril· sulfate.
White powdery substance
Melting point: 220-225°C.

By using 1.0 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril and 290 mg of fumaric acid, and treated by procedures similar to those employed in the case of preparation of the sulfate as mentioned above, and recrystallized from ethanol to yield 0.97 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril·fumarate.
White powdery substance
Melting point: 196-198°C.

By using 1.0 g of 7-{4-[4-(2,3-dichlorophenyl)1-piperazinyl]butoxy-3,4-dihydrocarbostyril and 290 mg of maleic acid, and treated by procedures similar to those employed in the case of preparation of the sulfate as mentioned above, and recrystallized from ethanol to yield 0.98 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril·maleate.
White powdery substance
Melting point: 172-180°C. It is also disclosed that this

This cited document also discloses about melting point and melting point of resulting compound aripiprazole is 139-139.5°C which is close to the claimed melting point of 140.7°C of anhydrous form B of aripiprazole. So cited document D1 gives an idea about aripiprazole and anhydrous form B of aripiprazole and their process of preparation.

Now I go through cite document D2 (US4734416). Cited document D2 also discloses about carbostyril derivatives and also about its salts. Claim 1 of this cited document reads as: "A carbostyril derivative represented by the formula, ##STR25## wherein R@1 is a hydrogen atom, an alkyl group having 1 to 6 carbon alkynyl group having 2 to 4 carbon atoms or a phenyl alkyl group having an alkylene group having 1 to 4 carbon atoms; R@2 is a hydrogen atom; R@3 is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms; R@4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms; R@5 is a phenyl group which may be substituted by 1 to 3 identical or different groups selected from the group consisting of a halogen atom, an alkyl group having 1 to 4 carbon atoms and an alkoxy group having 1 to 4 carbon atoms; X is a halogen atom; n is 0 or an integer of 1 or 2; Q is an integer of 2; l and m are respectively 0 or an integer of 1 to 6, but the sum of l and m should not exceed 6; the carbon-carbon bond at the 3- and 4-positions in the carbostyril skeleton in a single or double bond; the substituted position of the side chain of ##STR26## is any one of the 4-, 5-, 6-, 7- or 8-positions; or an acid addition salt thereof, with the proviso that when said side chain is substituted at the 4-position and said carbon-carbon bond at the 3- or 4-positions is a double bond, then R@2 does not exist. So aripiprazole and its salts are disclosed in this document.

Now I go through cited document D3. This document discloses about effect of grinding on physiochemical properties and polymorphs of Aripiporazole. This document discloses about polymorphs and effect of grinding on physiochemical properties of crystalline Aripiprazole. Type 3 crystals of aripiporazole of this cited documents is hydrate A of this instant application and type 1 crystal of this cited document is anhydride crystal B of this instant application. This document also discloses that Type III crystals were converted to Type-1 crystal by heating at 80degee C. So there is slight change in process temperature which is obvious to skilled person. So this cited document discloses about various crystal forms and also about two types of polymorphs.

Document D4 also discloses about Aripiprazole. Compound 28 of this document is aripiprazole. This document also discloses about dopamine receptor antagonistic activity. This document explicitly mentions the use of DA receptor antagonist as antipsychotic agents useful for treating schizophrenia, a current clinical use of Aripiprazole. This document also discloses process for preparing Aripiprazole and same has been prepared from a crude residue of a reaction in acetonitrile, which is extracted with ethyl alcohol.

Cited document D5 discloses about use of aripiprazole in treatment of schizophrenia.

This instant application also discloses a process of preparing different crystals. Hydrate A has been prepared by milling Conventional hydrate in an atomizer. Crystal B has been prepared by heating aripiprazole hydrate A. Crystal C, has been prepared by heating aripiprazole anhydride at particular temperature range. After heating at desired temperature range for a particular time period crystals are formed. For preparing crystal D, recrystallization of aripiprazole anhydride has been done from toluene. Crystal E has been prepared by recrystallization of

aripiprazole anhydride from acetonitrile. Type F crystal has been prepared by suspending aripiprazole anhydride in acetone and then heat the suspension above boiling point of acetone for 5 to 10 hours. After heating, F crystals have been formed and same has been separated by filtration. Type G crystals prepared by putting glassy state of aripiprazole anhydrine in a vessel and leave it to stant at room temperature upto six months.

So from the above said discussion following points are very clear: Aripiprazole and its various crystal forms are already known in the art. Process of preparing different crystals is also obvious to person skilled in the art. The process claims claimed a known product by submitting a known reactant to known conditions.

Before going to deal with other sections I would like to go through various pages of the specification. The specification starts with the line under heading "Detailed description of the invention": the present invention relates to an improved form of aripiprazole having reduced hygroscopicity and processed for the preparation of this improved form."

Further the specification describes: "According to Example 1 of Japanese unexamined patent Publication No. 1912656/1990, aripiprazole anhydride crystals are manufactured for example by reacting 7-(4-bromobutoxy)-3, 4-dihydrocarbostyril with 1-_2, 3-dichlorophenylpiperadine and recrystallizing the resulting raw aripiprazoile anhydride with ethanol. Also according to the Proceedings of 4th Japanese-Korean Symposium on Separation of Technology (October 6-8, 1996), aripiprazole anhydrides crystals are manufactured by heating aripiprazole anhydride crystals obtained by the aforementioned methods have the disadvantages of being significantly hygroscopic."[1st para of page 2]

The specification describes under the heading "SUMMARY OF THE INVENTION": "thus according to the present invention is provided a form of aripiprazole having reduced hygroscopicity and which is more amenable to hygroscopicity and which is more amenable to pharmaceutical processing and formulation. The inventors of the present invention have discovered that this reduced-hygroscopic form of Aripiprazole is a crystalline substance defined herein as Anhydride B."

Further the specification describes: "It was also discovered that a particular sequence of processing had to be implemented in order to form hydrate A. It was discovered that the preparation of Hydrate A required milling what is defined herein as Conventional hydrate. Then hydrate A can be transformed into Anhydride B through suitable heating as defined herein." {Page 4 last para].

Further the specification describes: "In course of research, they have found that the desired aripiprazole anhydride crystals can be obtained when a well-known aripiprazole anhydride is heated at the specific temperature. Further, the present inventors have found that the desired aripiprazole anhydride crystals can be obtained from recrystallization of a well-known aripiprazole anhydride by using the specific solvents. Moreover, the present inventors found that the desired aripiprazole anhydride crystals can be obtained by suspending a well-known aripiprazole anhydride in the specific solvent, and heating thus obtained suspension." [Page 5-6]

Now the first question is whether other crystal forms of aripiprazole having reduced hygroscopicity can be prepared by a skilled artisan or not? In my opinion, the answer to this question is yes. Aripiprazole and its different polymorphic forms and use in pharmaceutical industry are already known and already disclosed in cited documents and also background of the invention. So, in my opinion, it was well within the ambit of a skilled artisan at the time the present alleged invention was made, in order to try some more suitable hydrate, crystal forms to combine the knowledge of prior art documents and to arrive at the subject-matter of the instant alleged invention as claimed in the present claims, i.e., Hydrate A , anhydride crystals B, crystals C-G using Aripiprazole (already known) was obvious to try for a person having ordinary skill in the art in view of the teachings of cited documents. So finding of different crystal forms of already known compound, checking its hygroscopicity and stability does not involve any inventive step, because these are routine experimentation in the field of pharmaceutical chemistry which can be carried out by a skilled artisan easily. Those routine experimentations are well within the ambit of person having ordinary skill in the art without applying any inventive thinking. Further, it is well known that hygroscopicity, stability is physical property of crystal forms, which does not address the inventive step issue and hence, I opine that there is no contribution of the applicant to impose the said property to the claimed substance rather than it is inherent physical property for the same and applicant has gone through experimentation to assess the same only. Besides this, process of preparing crystal form A, anhydride crystal B, crystals C-G also obvious to person skilled in the art. Different process steps as disclosed in this application are-milling conventional hydrate, heating aripiprazole hydrate A at a particular temperature, dissolving in a solvent, recrystallizing from solvent. As I already discussed slight modification in process parameters (temperature, heating time etc) also obvious to skilled person. So said process steps are obvious to skilled person. So amended claims are surely lacking in inventive step and claims are not allowable under section 2(1) (ja) of the Act on the ground of lack of inventive step.

22.01Now I go through the last part of the submission of Opponent submitted after hearing: "The applicant only found an arguably different polymorph of the same compound in the impugned invention. Further on finding a different polymorph, determining its physical property is also obvious. The reduced hygroscopicity of anhydride B crystals of aripiprazole can be considered as an inherent property and not contributing to any inventive merit. Finding such crystalline form and testing its stability, bioavailability/dissolution is routine experimentation which can be carried out by skilled artisan easily. Also, the process of preparing anhydride B that is by heating hydrate A is obvious in view of the prior art."

The argumentation of Opponent regarding the inventive step is amply clear and also sufficient to establish their view regarding lack of inventiveness of claims. So I hold that since the submission of the opponent regarding inventive step is sufficient and so I opine that the opponents have been able to establish this ground properly.

GROUND SECTION 3(d):

23. Now I would like to discuss my view about section 3(d). As I already discussed the submission of both Applicant and opponent in above said paragraphs, now I want to

discuss my observation regarding the objection raised by the Opponent under section 3(d) of the Act. It should also be borne in mind before going through the discussion that Aripiprazole, 7-{4—[4-(2, 3-dichlorophenyl)-1-piperazinyl]-butoxy-3,4-dihydro carbostyril and its use in treatment of schizophrenia is already known. This instant application find/discovered another improved form of aripiprazole having reduced hygroscopicity. It is also to be noted that different crystalline form (type-I crystal, type-II crystal) of aripiprazole is already known in the art. I have thoroughly and carefully gone through reference Examples, examples as given in the specification. I have also checked NMR data, X-Ray diffraction data, IR spectrum data of different type of crystals form of aripiprazole such as aripiprazole anhydride crystal B, type C crystal, type D crystal, type E crystal, type F crystal and type G crystal as given in Examples. I also checked dissolution data as provided in Tables 1 to 6 of the specification.. In the written submission, the applicant submitted: "In the specification it is clearly mentioned that each of the aripiprazole forms of the present invention has reduced hygroscopicity, better solubility, more bioavailability and improved shelf life. Thus, such properties of the product of the present invention renders the compounds more superior to the prior art compounds." But no comparative experimental data has been shown in the instant specification to demonstrate superior therapeutic efficacy of the present claimed crystal forms of aripiprazole in comparison to the other known crystalline forms of Aripiprazole available in the prior art documents as discussed above. So the present claimed different crystalline form of aripiprazole definitely fall with the scope of the definition of mere new form of known substance as guided by Section 3(d) of the Act. To pass the test of Section 3(d), the new form of a known substance must demonstrate substantially enhanced therapeutic efficacy in comparison to the known compounds itself i.e aripiprazole. . The applicant's Agent submitted in the submission: "In the specification it is clearly mentioned that each of the aripiprazole forms of the present invention has reduced hygroscopicity, better solubility, more bioavailability and improved shelf life. Thus, such properties of the product of the present invention renders the compounds more superior to the prior art compounds." This is not persuasive. These are physical property of crystal form. No comparative experimental data has been shown in the instant specification to demonstrate superior therapeutic efficacy of the present claimed crystalline forms in comparison to other crystal Forms of said compound as disclosed in prior art documents in specification, dissolution data of different types of crystal have been given. So in the absence of any experimental data showing substantially enhanced therapeutic efficacy of the instant claimed hydrate or crystal forms in comparison to other polymorphic forms of the same compound as disclosed in this application, the present claimed crystalline Forms are actually mere new form of already known compound Aripiprazole as disclosed in cited documents given in the specification and thus are considered as same compound as taught by cited documents as per the "Explanation" part of Section 3(d) of the Act. Therefore, in my opinion amended claims are not patentable under section 3(d) of the Act. Therefore I decline to accept the argument of applicant in respect of Section 3(d). I conclude that reduced hygroscopicity, better solubility, more bioavailability and improved shelf life per se which are physical properties of the claimed crystal Forms should not be the criteria for establishing the present section and capable to overcome section 3(d) for the impugned application over the prior art. Hence, in my opinion, the different crystal forms as claimed in the presently amended claims have been unable to pass the test of Section 3(d). So I hold that since the submission of the opponent regarding section

3(d) is sufficient and so I opine that the opponents have been able to establish this ground properly.

In the present context I am skipping the discussion related to rest objections raised by opponent as the said discussion does not have meaningful and significant contribution to the same over the above mentioned paragraphs.

CONCLUSION:
Considering the pre-grant opposition, statements of both the parties, arguments during hearing and in view of my above findings I hereby accept the representation and refuse to grant of a patent on the Patent Application No. IN/PCT/2002/1536 and the said case is disposed of under section 25(1) of Patents Act and the corresponding Rules 55 of Patents Rule, 2003, as amended. There is no award of costs to either party.

24. However, after completion of hearing of pre-grant opposition, this application was re-examined based on the submission and observations given by the applicant with respect to First Examination Report (FER), this Office found that the observations given by the Applicant were not satisfactory. Thereafter, the Office offered the Applicant an opportunity of being heard on 30/11/2017 and the notice of hearing was sent to the Applicant by this Office on 10/11/2017. The following objections were communicated to the applicant:

- ✓ Subject matter of the invention as claimed in claims 1-97 lacks inventive step/non-obviousness in view of the following prior art documents.
  D1: EP 0367141 (A) (OTSUKA PHARMA COL TO) 9 May 1990 (09/05/1990)
  D2: SATOSHI AOKI ET AL: 'Study on Crystal Transformation of ARIPIPRAZOL' Proceeding of the 4th Japan-Korea symposium on Separation Technology, Tokyo, October 6-8, 1996, pages 937-940
  D3: YASUO OSHIRO ET AL: 'Novel Antipsychotic Agents with Dopamine Auto-receptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-d ihydro-2(1 H)-qui noli none Derivatives' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, val. 41, no. 5, 26 February 1998 (26/02/1998), pages 658-667, ISSN: 0022-2623
  D4: US 4734416 (A) 29/03/1988, D5-WO2004106322, D6-US5006528, D7-K.bauer et al "Pharmazeutische Technologie", Georg Thieme Verlag, Stuttgart, 1986, pages 75-81.

D1 discloses Aripiprazole and its salts. Further, it also discloses the process of preparation of aripiprazole by recrystallizing twice from ethanol and the resulting compound aripiprazole had a melting point of 139-139.5°C which is close to the claimed melting point of 140.7°C of anhydrous form B of aripiprazole.

D2 discloses (p. 938) anhydrous type 1 with amp of 140 degree C, prepared by recrystallization from ethanol. This can be converted to anhydrous type 2 with MP of 150 degree C by heating. Recrystallisation in wet alcohol gives hydrate type 3 (no mp given). Hydrate type 3 can be converted to type 1 by heating at 80 degree C.

D3 discloses that the compound 28 in Table 1 is Aripiprazole. Its dopamine receptor antagonistic activity is mentioned. The text of the document explicitly mentions the use of DA receptor antagonist as antipsychotic agents useful for treating schizophrenia, a current clinical use of Aripiprazole. On page 664 column 2, it is reported that Aripiprazole is prepared starting from a crude residue of a reaction in acetonitrile, which is extracted with ethyl acetate, it is washed and dried in vacuo and finally recrystallized from ethanol.

D4 also teaches aripiprazole and its salts.

Of the cited prior art documents, only D2 discloses aripiprazole as the hydrate. Hydrate A is defined in claim 1 by its powder x-ray diffraction spectrum, by characteristic IR absorption bands, by its endothermic curve and by a mean particle size of 50 microns or less. D2 does not mention the particle size obtained by recrystallization from ethanol-water.

D3, compound 28, D1, ex. 1 and D2, type 1 appear, from the preparation method and melting point, to relate to the same compound (possibly at slightly differing levels of purity), which is considered the closest prior art.

Anhydride B is defined by hygroscopicity parameters, by its powder x-ray diffraction spectrum, by characteristic IR absorption peaks and by endothermic peaks. No comparison of the IR spectra or endotherms is presently possible as such data is not present in D1-D3 or on file. Without such data these characteristics cannot be considered to be distinguishing features. The powder xray diffraction spectrum in present Fig. 5 appears to be substantially identical to D2, Fig. 3a). It thus remains to

compare the hygroscopicity data obtained from anhydrides according to the processes of D1-D3 and that obtained according to examples 2-15 of the present application. The applicant has prepared an anhydride in reference example 1, in which crude aripiprazole is recrystallized once from ethanol, to give a compound with amp of 140 degree C and a hygroscopicity of 3.28%. In reference example 2, conventional hydrate is dried at 80 degree C for 30 hours to give a compound with amp of 139.5"C and a hygroscopicity of 1.78%. It is noted that D1 describes recrystallization twice from ethanol, which has not been reproduced in the reference examples. There is thus no evidence at present to show that the more highly purified product of D1 has hygroscopicity above the threshold given in present claims.

D5 discloses polymorphs of Aripiprazole. Also discloses about DSC XRD data.

Also consider documents D6 and D7 for inventive step.

Further, a person skilled in the art can arrive at the present crystalline/polymorphic forms of the Aripiprazole and the pharmaceutical preparations based thereof in view of the above cited documents. The processes are also looking obvious in view of the above cited documents because these are normal crystallisation process as well as similar processes are also disclosed in the cited documents.

Moreover, the applicant does not provide any enhance technical data in the form of therapeutic efficacy of the present crystalline forms of Aripiprazole over the cited polymorphic/crystalline forms.

The subject matter of claims 1-97 therefore does not involve an inventive step in view of the above cited documents.

Hence the invention is not patentable under section 2(1)(ja) of The Patent Act 1970.

- ✓ Claims of the present application attract the provision of section 3(d) of the Act as the present application defines several crystalline/polymorphic forms of the Aripiprazole. The Aripiprazole is already known from the above cited documents. Further, the documents D1-D3 also disclose several crystalline/polymorphic forms of the Aripiprazole and process for preparation thereof. Moreover, the applicant does not provide any enhance technical data in the form of therapeutic efficacy of the present crystalline forms of Aripiprazole over the cited polymorphic/crystalline forms.

- ✓ Further, the subject matter of the claims 28-31, 39-49, 52-55, 71, 77-95 of the present application attracts the provision of section 3(e) of the Act in absence of any synergistic effect.
- ✓ The instant application contains several independent products as well as process claims. These claims are related to the different crystalline forms, their pharmaceutical preparation and process for preparation thereof. Moreover, these claims does not relate to a single inventive concept for the following reasons:

  The only common feature between these claims appears to be the fact that aripiprazole or a composition thereof. Not only does this feature have nothing in common with the special technical feature of claims, it is also not new (see D1-D4). Thus the common feature of claims cannot be considered to be the special technical feature. Hence each independent claim appears to form a separate invention according to the section 10(5) of the Act.
- ✓ The expression/terms "substantially", "about", "one or more" before any inventive feature or any value in claims make the claims unclear and vague. Hence these terms cannot be allowed in the claims.
- ✓ The term "anhydrous" as used in claims also not supported by description and beyond scope of claims as originally filed and not allowable under section 59(1) of the Act.
- ✓ Drawing should be submitted in prescribed format according to section 10 and rule 15 of The Patents Act, 1970 & The Patent Rules, 2003 with full name of the signatory authority.
- ✓ The name of the signatory in the Form-18 should be mentioned
- ✓ The proof of right in the form of endorsement or assignment from the inventor has not been filed yet according to u/s 7(2) of The Patent Act, 1970. The same should be filed in the prescribed manner with required petition.
- ✓ Form 1 has not been filed in prescribed format for the following reason:

  a. The details of inventors should be given in prescribed format.

  b. The declarations as scheduled in col- iii of paragraph 9 of the Form-1 have not been given by either affirming or cancelling out the all heads (mandatory requirement). Hence, a fresh form 1 should be filed in prescribed manner.

- ✓ Form-5 (Declaration of Inventor ship) has not been filed in prescribed format. Hence it should be filed in prescribed format according to the section 10(6) & rule 13(6) of the Act.
- ✓ Any kind of handmade correction or using whitener in any forms or in specification cannot be allowed without proper endorsement.
- ✓ The complete specification has not been filed in the prescribed manner. a. Blank space in any page of the specification should be scored out. b. The complete specification does not satisfy the rule 9(1) of the Patent Rules, 2003. C. Numbering of the pages should be started from the first page (Form-2) of the specification. Hence these should be rectified.
- ✓ Details regarding application for Patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within Six months from the date of filing of the said application under clause(b) of sub section(1) of section 8 and rule 12(1) of Indian Patent Act.
- ✓ Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent office's such as USPTO, EPO and JPO etc., along with appropriate translation where applicable, should be submitted within a period of Six months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.
- ✓ Applicant should file English translated copy of the priority documents duly verified by the applicant or the person duly authorized by him with required petition according to the rule 21(3) of the Act.
- ✓ The Preamble of claim should be replaced by "I/We Claim" according to the section 10 & rule 13 of The Patent Act – 1970 & The Patent Rule 2003. So, it should be corrected in prescribed manner.
- ✓ The invention as disclosed in the specification uses the biological materials (corn starch, cellulose, etc.). Hence the source and geographical origin of the biological material should be disclosed in the specification. If the biological material is obtained from India then, the necessary permission from the competent authority should be taken.

25. After the hearing, the applicant submitted the written note of arguments on 06/01/2018.

26. For objections raised under para 1 of the hearing letter, the Applicant submitted their view. For judging the inventive step, I go through the cited documents as given in hearing notice.

Cited document D1 discloses Aripiprazole and its salt. It also discloses process of preparing aripiprazole by recrystallizing twice from ethanol. The compound obtained after recrystallization had a melting point of 139-139.5 degree C, which is close to the melting point of anhydrous form B of ariprazole. Document d2 discloses anhydrous type-1 with amp of 140 degree C and this can be prepared by recrystallizing from ethanol. Type-1 crystal can be converted to type-2 crystal by hearting. Similarly recrystallization in wet alcohol produce hydrate type-3 and this can be converted to type-1 by heating at 80degree C.

Document D3 also discloses that the compound 28 in Table 1 is Aripiprazole and this document also discloses about its dopamine receptor antagonistic activity. This cited document explicitly mentions the use of DA receptor antagonist as antipsychotic agents useful for treating schizophrenia, a current clinical use of Aripiprazole. On page 664 column 2, it is reported that Aripiprazole is prepared starting from a crude residue of a reaction in acetonitrile, which is extracted with ethyl acetate, it is washed and dried in vacuo and finally recrystallized from ethanol.

Document D4 also teaches about aripiprazole and its salt.

Document D5 discloses about new polymorphs of Aripiprazole an also about XRD data. This document discloses about process for preparing polymorph of Aripiprazole by contacting crude aripiprazole in suitable solvents, solvent may be isopropanol; methanol etc at elevated temperature and then cools the solution and removes the solvent.

Document D6 teaches about carbostyril derivatives and their salt.

So from the cited documents of hearing notice, it is clear that compound aripiprazole and its different forms (hydrate, crystal), and use as medicine is already known. Now the question is whether a skilled artisan can able to prepare other crystal Forms from the teachings of the cited documents or not? In my opinion, the answer to this question is yes.

So from the discussion in the above said paragraphs and also from the cited documents, this is very clear that aripiprazole and its different crystalline forms and their use in treatment of schizophrenia is very well known in the art. It is a common general knowledge for skilled person in this field that a substance when investigated for a long time then more than one polymorph can be found. So, in my opinion, it was well within the ambit of a skilled artisan at the time the present alleged invention was made, in order to try another suitable crystal forms to combine the knowledge of prior art documents and to arrive at the subject-matter of the instant alleged invention as claimed in the present claims, i.e., hydrate, anhydrous crystals were obvious to try for a person having ordinary skill in the art in view of the teachings of cited documents. A skilled person can able to find other crystal form of a known compound (here it is aripiprazole), because there is a clear hint in prior art documents as discussed above

and also systematic investigation of polymorphism of known compound is routine practice in this field. So finding of other crystal forms of already known compound, checking its hygroscopicity, shelf-life, stability does not involve any inventive step, because these are routine experimentation in the field of pharmaceutical chemistry which can be carried out by a skilled artisan easily.

I also go through the process claims and I find that processes of preparing of different crystals are obvious to skilled person. Hydrate-A crystals prepared by milling aripiprazole crystals ,aripiprazole anhydride crystals B prepared by heating aripiprazole hydrate A, Type-C crystals were obtained by heating anhydrous aripiprazole crystals at a temperature higher than 140 degree C, Type-D crystals were prepared by recrystallization of aripiprazole anhydride from toluene, Type-E prepared by adding a well-known Aripiprazole anhydride to acetonitrile, heating and dissolving, then the solution thus obtained solution is cooled. Type-F crystals were prepared by suspending aripiprazole anhydride in acetone and refluxing with stirring. The crystals thus obtained were air dried. Last, Type-G crystals of aripiprazole anhydride were obtained from glassy state of aripiprazole anhydride. Here the starting material (aripiprazole) is already known and all the said process steps are also known in art and obvious to person skilled in the art. Process of preparation of granules, process for the pharmaceutical solid oral preparation of granules are also well-known.
Now I would like to discuss about one of the findings of Hon'ble IPAB regarding obviousness. IPAB Order No.-224/2010 wherein IPAB has observed that "a patent application has to be accessed on the basis of not only what will be available from prior documents but also from the common general knowledge on the subject, which may or may not be available in any such document. It can be taken as a well settled principle, that the common general knowledge is a knowledge that must be attributed to a skilled person, without which he may not be taken to be a skilled person in the art" (see page-37 of IPAB order 224/2010).
So from the teachings of cited document and also from common knowledge a person skilled in the art can be able to prepare different type of crystals of aripiprazole. So amended process claim submitted after hearing also lacking in inventive step and not allowable under section 2(1) (ja) of the Act.
As claims are lacking in inventive step and also not allowable under section 3(d) of the Act, so I do not want discuss about section 3(e) of the Act.

27. For objection regarding section 3(d), the Applicant submitted their view but I have already discussed section 3(d) in my discussion under paragraph 23, so there is no need to repeat it again. So the objection is still not met.

28.For other objections raised under para 4-18 of the hearing letter the Agent of the Applicant submitted their view and also deleted objected terms and objected claims, submitted a petition under rule 137 for not submitting proof of right in time, submitted fresh Form-1, Form-5, updated schedule. So the objections are now met.

ORDER:

Having considered all the facts and submissions made by the Agent of the Applicant during hearing and in the written note of arguments as well as in view of all the documents on record and also on the basis of my analysis and findings as mentioned in the preceding paragraphs, it is found that the objections raised under paragraphs 1, 2 of the hearing notice as mentioned above have not been complied with by the Applicant. Therefore, based on the above facts and submissions, I hereby also refuse to proceed further with this instant patent application number IN/PCT/2002/1536 for grant of patent under Section 15 of the Patents Act, 1970 (as amended).

Dated this 20th day of February 2018.

Bhaskar Ghosh

(Bhaskar Ghosh)
Dy. Controller of Patents & Designs

Copy to:

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