
Stability per se of a Salt not a Patentable subject matter

This article summarises the recent decision of Indian Patent Office on a pre grant opposition filed by Lupin Ltd, a well known Indian Pharmaceutical Company (hereinafter Lupin) against application no. 3176/Kolnp/2007 of Mitsubishi Pharma Corporation (herein after referred as Mitsubishi). The Controller ruled in favour of Lupin rejecting the grant to the patent on the grounds that the Invention lacked Inventive step and was not an Invention within the meaning of section 3(d) of the Patents Act .

Brief facts of the case:

1. Mitsubishi filed a patent application for the Invention titled "Salt of proline derivative, solvate thereof and production method thereof".
2. The claims of the patent application as filed covered salt of 3-{ (2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine -referred as *Teneligliptin* hereinafter or solvate thereof, in further claims 2.5 hydrobromide of *Teneligliptin* or a solvate thereof and in more further claims 2 hydrobromide of *Teneligliptin* or a solvate thereof.

Lupin argued for refusal of Patent on the following grounds

- a) Anticipation;
- b) Lack of Inventive Step; and
- c) Invention hit by section 3 (d) on account of lack of therapeutic efficacy.

The grounds and arguments of both the parties are summarised below:

Lupin's Arguments

- a) Lupin relied on the corresponding US application (referred as [D1-US2004/0106655](#) of the applicant's self acknowledged WIPO patent application WO2002014271 in the background section, for substantiating the ground of anticipation.
- b) D1 admittedly teaches the compound Tenegliptin, its pharmaceutically acceptable salt including inorganic acid addition salt e.g. HCl, HBr etc. and its method of production. D1 in example discloses 3HCl salt and so there is no speciality in the salt preparation of HBr or 2.5 HCl.

- c) The specification and claims do not make any distinction between the salts and there is nothing to prove anywhere in the alleged invention that the salts of D1 would not provide similar result for all the salts mentioned.
- d) Lupin further relied on [D2 \(US2004/0259883\)](#) which it alleged, teaches similar compounds as that of Teneligliptin, particularly Teneligliptin 3 HCl. It also discloses acid salts of the Teneligliptin and the possibility of polymorphism. For the claim on method preparation of Teneligliptin, Lupin stated that there is nothing in the process except combining known teneligliptin with hydrobromic acid and elimination of protecting group.
- e) Lupin relied on yet another document D3 (a non patent literature by Gould, P.L. "Salt selection for Basic drugs" International Journal of Pharmaceutics, 33 (1986), 201-217, which outlined the general teaching about salt selection of Basic drugs providing list of acids with which salts are formed for various drugs. D3 mentioned the problem arising with HCl salt due to high polar nature which favours wettability and leading to hygroscopicity and the processibility problem. Lupin argued that D3 discloses hygroscopicity of dihydrochloride is more than monohydrochloride also HCl being more polar than HBr.
- f) Lupin also pointed out that the impugned invention related to all salts while only during the opposition it was restricted to 2.5 HBr. Thus, all the properties which were said to be similar in all the salts including the HCl salt in the specification cannot be denied on the aftermath of the opposition. Thus, the properties of HBr highlighted during opposition were originally disclosed as belonging to any or all salts mentioned.
- g) Lupin relying on section 3(d) argued that Teneligliptin, its salts and the associated polymorphism phenomenon is known from the prior art. The inventors only prepared certain forms like 2.5HCl, 2.5HBr and their solvates/hydrate which have defined XRD peak values to indicate crystal forms. The invention fails to provide the therapeutic efficacy and thus falls under section 3(d) therefore non-patentable. There is no data in the specification to show that all the salts as claimed provide advantages in terms of stability, hygroscopicity and solubility etc. There is no data to show the synergistic property and the comparative data to demonstrate that there is improvement over the admittedly known salt of Teneligliptin.

Mitsubishi argued:

- a. The stability, bioavailability, reproducibility of HCl salt was not good and could not be formed into crystals. Mitsubishi unexpectedly found that 2.5 HBr salt could form crystals and were stable.
- b. D1 being admittedly closest prior art but it provides markush type of compounds while the present application is focused on the selection of 2.5 HBr.

- c. Since there is problem with forming crystals of HCl, thus no person would try HBr as it is known that what is applicable to HCl will be applicable to HBr. Thus, it is unexpected to achieve crystals with HBr.
- d. Even if HCl salt is obtained in the prior art it does not mean that HBr salt will also be obtained in the same manner and that crystallization of HCl being difficult, it would not be predictable that HBr salt and that in a crystalline form can be formed.
- e. The Inventors tried crystallization of 3HCl salt of Teneiglipitin as described in the example of D1 but could not obtain the same
- f. Crystallization of HCl being a difficult process would not hint that HBr salt (and in the crystallized form) could be prepared by the same process.
- g. The properties of better stability, bioavailability, less hygroscopicity were lacking in the prior art compounds and D1 discloses the powdered form of 3HCl which is not in the crystal form.
- h. Mitsubishi also submitted experimental data to demonstrate the better stability, less hygroscopicity and crystallinity of 2.5 HBr.
- i. Mitsubishi showed that the salt of the invention has no toxicity and can be used safely- thus contributing towards the therapeutic efficacy.

Controller's Decision:

- The Controller referred the teaching of D1 to conclude that Teneiglipitin compounds and its salts were disclosed and stated that specification is devoid of any comparative experimental data on the therapeutic efficacy of the claimed salt over the prior art compounds. In order to overcome the undesirable properties of the prior art salt with regard to the stability, hygroscopicity, the present invention emerges but the same does not provide any comparative data to show any technical advancement of such salts and solvates.
- The method of preparation of 2.5 HBr salt of Teneiglipitin involves regular method of preparing the salt and there is no mention in the specification about the therapeutic efficacy to indicate the solubility and hygroscopicity of the compound.
- The Controller also stated that there is no contribution of the Mitsubishi to impose the physical property like stability to a particular crystalline form of a compound as that is the inherent property of that compound.

- The Controller also relied on the teaching of D2 mentioning that the document teaches that HCl salt being more polar is more hygroscopic and increasing stability reduces hygroscopicity. Thus, it is obvious to conclude that HBr salt is less hygroscopic and more stable with regard to HCl salt.
- With respect to section 3(d), the Controller stated that the application does not show the efficacy particularly therapeutic efficacy of the compounds claimed. There is no acceptable experimental data with regard to already known prior art compound except for solubility and hygroscopicity
- There is no support with experimental data for the claim of low toxicity, stability issue. The Controller further state that stability per se cannot be a patentable subject matter until and unless it has substantial efficacy, more precisely therapeutic efficacy substantiated with the comparative clinical data.
- The solubility and hygroscopicity per se which are the physical properties are not the criteria to overcome section 3(d)

Key takeaway Points:

- a) A patent application having claims on a solvate /salt/ hydrate/ derivative or any other form of a compound is likely to invite objection under section 3 (d). Thus, the patentee in order to cross the barrier of section 3(d), must produce comparative experiments (with the prior art) in the specification to substantiate the enhanced therapeutic efficacy.
- b) While writing the specification, the patentee must be very careful about what he is admitting or acknowledging (in the background section) as the scope of prior art plays important role while judging the inventive step of the subject invention.

Thus, in case of derived forms/salt/other forms, it is highly recommended to furnish experiments and comparative studies that can help to show enhanced therapeutic efficacy for overcoming section 3(d).

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