In our constant endeavor to bring better insights for our clients and friends on the practice of Patents at the Indian Patent Office, we are pleased to bring a series of Case Studies on the interpretation of 'efficacy' for meeting the requirements of Section 3 (d) of the Indian Patents Act, 1970 for grant of Patent. Here is the first of the series:

Revisiting Efficacy: Case Study I

Section 3 (d) of the Indian Patent Act has generated quite a buzz in recent times at various Intellectual Property forums and events, where the debate has been on the different treatment and interpretation of the requirement of 'enhanced efficacy' by the examiners, controllers and the judicial officers while deciding on the patentability of Chemical entities which may be classified as 'new form of known substance'.

Section 3 (d) of the Act has recently been hotly debated in the International arena in wake of the recent decision by the Supreme Court of India on an anticancer drug known as 'Gleevec'. This Court held that the Beta form of imitinib mesylate is *'a new form of a known substance and 30% enhanced bioavailability of this form alone cannot be considered enhanced efficacy* in view of lack of adequate research data' However, the court categorically held that the efficacy has to be judged on a case to case basis and this case cannot form a precedent for any other case. his article is the first of the series of 'an analysis of decisions on 3 (d) rejections/acceptances' which may help our readers in adopting suitable strategy in overcoming the rejections under this section.

The present decision was rendered by Controller of Patents & Designs on 26th December, 2012, i.e. approx. six months before The Indian Supreme Court decided on the 'Gleevec case'. Applicant in this case was Alfa Wassermann of Italy and the application was a divisional of another Indian application corresponding to PCT/EP2004/0112490.

In order to remain within the topic, the discussion is limited to the grounds of rejection citing section 3 (d) only. The present patent application described and claimed a new form of Rifaximin, designated as 'beta form' and the methods to produce the form. Rifaximin is a semisynthetic antibiotic based on rifamycin. According to the prior art, this drug has poor oral bioavailability, and very little of the drug is absorbed into the blood stream when it is taken orally. Rifaximin is used in the treatment of traveler's diarrhea and hepatic encephalopathy. In the United States, Salix Pharmaceuticals holds the US Patents for Rifaximin and markets the drug under the name Xifaxan, available in tablets of 200 mg and 550 mg *(US Patent numbers: 7045620, 7612199, 7902206, 7906542, 7928115, 8158644, 8158781 and 8193196)*

The case

In the present case, the examiner initially rejected the claims under section 3 (d) and observed that the claims merely defined a new form (polymorphic form beta) of a known substance, rifaximin with no enhancement in the known therapeutic efficacy of that substance. It was further alleged that in absence of experimental data, it was not clear if the substituted derivatives of the said compound and the composition thereof act to provide *an enhancement of known efficacy* i.e. demonstrate a greater technical effect and/or differ significantly in properties w.r.t. known compounds.

The applicant, in order to overcome the rejection, interestingly, submitted during the hearing that, Rifaximin beta is 'selectively absorbed' in the intestine [only] whereas the known forms of the molecule are also absorbed in gastric tract making them unsuitable for targeted drug delivery. In its arguments, the applicant also submitted the unexpected properties of rifaximin in terms of its absorption kinetics. The comparative data provided by the applicant showed different pharmacological properties of different polymorphs of rifaximin.

It is interesting to note that in present application also the bioavailability of the drug formed basis of the arguments presented by the applicant in favour of their claims. However, in an important twist unlike the Novartis case, the drug in this application had selective bioavailability which was highly imperative as the known forms were rendered nearly ineffective due to their absorption in the gastric tract itself before reaching the intended target i.e. the intestine. This feature of the known substance made it indispensible and it sailed safely above the bar of efficacy of section 3(d) of Indian Patents Act.

The Controller agreed with the applicant's submission that 'a composition is new, if the compound used in it has improved pharmaceutical properties' and to the submissions made regarding the enhancement in efficacy. It is important to note that the Controller agreed to applicant's assertion that the present case does not fall under 3 (d) and the controller may wait up to the time when the present invention is challenged in any opposition/revocation proceeding.

Our Comments

Efficacy is the capacity to produce an effect. It has different specific meanings in different fields. While dealing with the Novartis' claim of a 30% bioavailability and submission that this is 'increased therapeutic efficacy', the Madras High Court has held that the term "enhancement of known efficacy" is not vague, and the term "efficacy" meant therapeutic efficacy. This interpretation was further affirmed by the Supreme Court and while deciding the appeal from the same case it was further clarified that whether or not increase in_bioavailability leads to enhancement of therapeutic efficacy in any given case must be specially claimed and established by research data.

Going by the meaning for the word "efficacy" and "therapeutic" extracted above, an applicant is expected to show how effective the new discovery made would be in healing a disease / having a good effect on the body. This means that the said new form of a drug should elicit a therapeutic effect by minimization of dose and lowered side effects.

It is also important to note that an increased bioavailability may result in increased toxicity also. Hence, would a lowered toxicity (which might be a result of low absorption/low bioavailability) mean increase in therapeutic efficacy? The present

case shows that the patent office may accept selective absorption or low toxicity as an indication of enhanced efficacy if substantiated by research data . It may therefore be said that to overcome the rejections placed under section 3 (d), one may consider providing the necessary data for proving enhanced 'therapeutic efficacy', which may include selective absorption at a particular site or even low toxicity as evidenced by the animal studies.

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