



Prima facie obviousness of pharmaceutical patents implications for enantiomers

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ABSTRACT

Innovator pharmaceutical companies file primary patents to protect new molecular entities (NME) and secondary patents to protect NMEs in various forms. "Non-obviousness" is the most critical criterion for patentability of both. A showing of "prima facie obviousness" shifts the onus to the patentee to prove that the claimed invention is non-obvious. This paper presents a framework to analyze the non-obviousness of the claims. More particularly it explains why the enantiomers are always prima facie obvious and how to overcome the same. The utility of the framework is demonstrated by analyzing the non-obviousness of Levofloxacin and other enantiomers.

1. Introduction

According to the Latin English, the word "Prima facie" means "at first appearance". The term prima facie is a terminology used in law mainly to signify that sufficient evidence appears to exist on initial examination. In most legal and court proceedings, prima facie denotes that there is sufficient evidence to establish a particular proposition unless it is rebutted, following which proceedings may then commence to test it, leading to a ruling [1].

In evaluating the non-obviousness of a patent application as mandated by 35 U.S.C§103 the examiner at the United States Patent and Trademark Office (USPTO) follows the standards laid down in USPTO's Manual of Patent Examination Procedure (MPEP) following the Supreme Court decision in *Graham v John Deere* [2] and *KSR v Teleflex* [3]. 35 U.S.C§103(a) states that "a patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." Further, MPEP guidelines require that, to make any rejection under 35 U.S.C§103 a clear articulation of why the claimed invention would have been obvious should be made [4]. This guideline is same for all technological fields but it assumes greater significance in chemical and pharmaceutical fields in view of the close similarity between the claimed structures *vis a vis* those in the prior art.

Following the US Supreme Court's KSR decision, United States

Patent and Trademark Office's Manual of Patent Examination Procedure (MPEP) demands that the examiner conducts the Graham inquiry to determine non-obviousness of a claim. Further a patent examiner may reject a claim by a showing of prima facie obviousness if the examiner finds a prior art sufficiently close to the claimed invention. This shifts the onus to establish non-obviousness to the applicant who can then, either reject the same by challenging the choice of the prior art or rebut it based on the absence of a teaching, suggestion or motivation in the prior art, reasonable expectation of success, etc.

The determination of the ultimate non-obviousness of an invention involving a showing of prima facie obviousness invokes a number of factors and requirements as laid down by the patent office and the courts respectively. Overcoming prima facie obviousness is the first step during the grant of a claim and during invalidation of a granted claim. We present a framework to evaluate prima facie obviousness as well as ultimate non-obviousness of claims in pharmaceutical industry in general and particularly in the case of enantiomers based on the analysis of various patent suits.

2. Discussion

2.1. Evolution

The prima facie obviousness in chemical arts was raised as early as in *In re Hass* (1944) when the United States Court of Customs and Patent Appeals (C.C.P.A) rejected the claims pertaining to certain alkyl nitro olefins as obvious over the prior art homologous compound [5]. The

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court in this case stated that even though the claimed homologous derivative was novel, it would not be patentable in the absence of a showing of some unobvious or unexpected beneficial properties not possessed by the prior art homologous compound. Similarly in *In re Henze* (1950), a hydantoin derivative was deemed obvious in view of a research publication [6] disclosing a structurally similar lower homologue of hydantoin. The applicant tried to overcome the obviousness by providing details of the therapeutic use and lower toxicity of the homologues at the claimed dosage. However the courts denied to accept this evidence in the absence of a showing by the applicant that the structurally similar prior art compounds did not possess the same characteristics [7]. These two cases established the Hass-Henze rule according to which once the examiner establishes that he has found a sufficiently close prior art to the claimed invention, the burden then shifts to the applicant, to establish non-obviousness by presenting relevant arguments or data to support the showing. Such evidences might include i) a showing of some unobvious properties in the claimed compound or ii) the absence of such properties in the prior art compound.

On the basis of Hass-Henze rule the applicant in *In re Papesch* (1963) provided evidence to show the absence of an unexpected property in the prior art compound by illustrating comparative examples wherein the claimed compound was an active anti-inflammatory agent while the prior art compound was completely inactive. The applicant also stated that in case of chemical compounds, the properties of the claimed compounds must also be compared with those in the prior art rather than the structure alone [8]. This case led the courts as well as the examiners to evaluate the invention “as a whole” in chemical arts i.e. the compound along with its properties. The courts also clarified that the properties such as respective chemical structures, uses and pharmacological trials of the new compound can be compared with the prior art while determining the obviousness of chemical compounds under § 103 [9].

This practice of evaluating “the compound along with its properties” was applied to determine the non-obviousness of a composition comprising tetraorthoesters for reducing the particulate emissions from fuels in *In re Dillon* (1990) [10]. Based on a prior art hydrocarbon fuel composition comprising tri-orthoesters for dewatering the fuels [11] and a three-component composition of hydrocarbon fuels wherein the triorthoesters were used as co-solvents to prevent phase separation between fuel and alcohol [12], the courts deemed the claimed invention prima facie obvious for two reasons i) structural similarity between the claimed tetra-orthoesters and the tri-orthoesters and ii) use of the known tri-orthoesters in oil arts. Further the court presumed tri-orthoesters known in the prior art to possess the claimed particle reducing property in the absence of evidences illustrating that the prior art compounds did not possess these properties. Thus applicants in this case were not successful in rebutting the prima facie obviousness by a showing of unexpected or improved properties of a claimed composition or the absence of such a property in the prior art composition.

In *In re Oetkar* (1992) the patent appellate board opined that the prima facie obviousness issue can be raised during patent prosecution in all technological fields [13]. The evidence submitted to rebut could be in the form of declarative submission based on any experimentation, if needed, to establish that the difference between the claimed invention and the prior art did not exist at the time of the claimed invention [14]. The board in *In re Oetkar* further clarified what constitutes prior art in order to reject a claim based on prima facie obviousness. Oetkar's claimed invention related to an open clamp structure with preassembly hook. The prior art as retrieved by the examiner included a hose clamp described in an earlier patent granted to the inventor himself and a second prior art describing a plastic hook and eye fastener for use in garments. According to the examiner the claimed invention was prima facie obvious over the combination of the two. The applicant in response, objected the improper combination of prior art. In its decision, the court stated that all hooking problems were analogous art and

hence the prior art describing a plastic hook and eye fastener for use in garments would constitute relevant prior art. While commenting on what analogous art is, the court also required the presence of some reason, teaching and suggestion in the prior art which would have reasonably motivated a person of ordinary skill seeking to solve a similar problem. The court further stated that although the hooking problem of the claimed invention and the prior art were analogous, the absence of a teaching suggestion or motivation to combine did not exist and hence the claimed invention was not prima facie obvious.

In summary while prima facie obviousness can be a ground for the rejection of a claim across all technological fields, the prior art for rejecting a claim needs to be chosen carefully. Such references may be from the applicants own field of research or from a field which is reasonably pertinent to the particular problem which the inventor was trying to solve [15]. This was practiced by the courts and PTO until Supreme court in its *KSR v Teleflex* (2007) opinion held that while the teaching suggestion motivation test provided a valuable guideline, it could not serve as rigid and sole test to ascertain non-obviousness of the invention and advocated a more expansive and flexible approach as originally envisioned in its *Graham v John Deere* (1966) decision. Supreme Court further said “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination yielded anticipated results might show that it was obvious under §103. Federal circuit decisions post-KSR reflected the inclusion of prior art from different technological areas in determining the ultimate obviousness of a claimed invention specifically when the problem solved by the claimed invention and the prior art were similar.

2.2. Prima facie obviousness: a framework

The patent lawsuits involving chemical and pharmaceutical inventions were collated from various legal information sources such as Lexology[®], Finnegan[®], Supreme Court Cases™ etc. The keywords such as non-obviousness, obviousness, prima facie case were combined with terms such pharmaceuticals, new chemical entities, enantiomers, combinations etc using the “AND” operator. Further the cases litigated in the United States courts were selected since the focus of the study was on US patent law. From this dataset the lawsuits which involved arguments relating to prima facie obviousness were shortlisted for further analysis. The case laws which were cited in the lawsuits and relevant to prima facie case of obviousness for chemical and pharmaceutical inventions were also considered for analysis. The prosecution history of the corresponding patent applications was also considered for analysis. Based on the analysis of these patent suits we propose a framework for evaluating prima facie obviousness and ultimate non-obviousness of a claim. This is illustrated in Fig. 1. The first step is application of the Graham factors. Based on this, if an examiner or a challenger finds prior art disclosing the elements of the claimed invention and presents reasoning to show that the claimed invention would be obvious in light of the prior art, then the prima facie obviousness can be raised (A). In the absence of this, rejection for prima facie obviousness cannot be raised and the invention is likely to be ultimately non-obvious (B).

Once a rejection for prima facie obviousness is raised, the burden of establishing non-obviousness shifts to the applicant who can reject the showing (C) by establishing that 1) the prior art cited by the examiner is not relevant and/or 2) there is no teaching suggestion or motivation in the prior art to arrive at the present invention. If an applicant fails to do so then, it sustains (D). At this stage, a rejection based on obvious to try rationale could be raised (F). If the applicant does not or cannot rebut the prima facie obviousness, it would sustain and the invention will ultimately be not non-obvious (E). If the applicant responds, he will

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