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State of Israel
Commissioner of Patents, Designs and Trademarks

Opposition to Patent Application
No. 172563

The Opponent: **TEVA PHARMACEUTICAL INDUSTRIES LTD.**
By counsel S. Horowitz & Co.

The Applicant: **MERCK SHARP & DOHME CORP.**
By Counsel Liad Whatstein & Co.

D E C I S I O N

1. I have before me the opposition of Teva Pharmaceutical Industries Ltd. (hereinafter: "**Teva**" or the "**Opponent**") to Patent Application no. 172563 (hereinafter: the "**Patent Application**" or the "**Application**"), which was filed by Merck & Co., Inc., USA (hereinafter: "**Merck**" or the "**Applicant**").

2. The Patent Application was filed on April 18, 2008, and it is entitled: "Phosphoric acid salt of dipeptidyl peptidase IV inhibitors". The application claims priority on the basis of Provisional Application No. 60/482161 (hereinafter: the "**Provisional Application**"), which was filed in the United States on June 24, 2003 (hereinafter: the "**Priority Date**" or the "**Effective Date**").

3. The Application was published in Patents Journal 7/2008, and the Opponent notified of its opposition to it on October 6, 2008.

Background

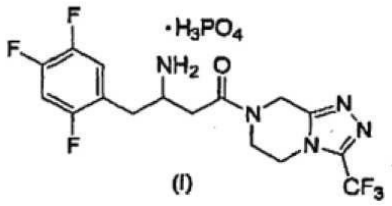
4. The Application claims a dihydrogen phosphate salt as well as a monohydrate crystalline form of the same salt of the active ingredient known as 4-oxo-4- [3-(trifluoromethyl)-5,6-dihydro[1,2,4] triazolo[3,4-a]pyrazine-7(8H)-yl]-1-2(2,4,5-trifluorophenyl)butan-2-amine, which will hereinafter be referred to as "**sitagliptin**". Sitagliptin is a compound that has an inhibitory activity on the enzyme dipeptidyl peptidase-IV (DPP-4), an activity which, according to the Patent Application, constituted a new approach in the treatment of type-2 diabetes.

5. The application includes 26 claims, one of which is independent, as stated below:

Claim No. 1 claims the dihydrogen phosphate salt; Claims 2 and 3 claim the salt which is the subject of Claim 1, where the chiral center of the molecule has an (R) configuration and an (S) configuration, respectively; Claim 4 claims the salt which is the subject of Claim 1, when it is characterized as a monohydrate crystal; Claims 5 to 11 claim the salt which is the subject of Claim 4, having different characteristics; Claims 12 to 17 claim a medicinal substance comprising various weight concentrations of the crystal that is the subject of Claim 4; Claim 18 claims a pharmaceutical composition comprising a therapeutically effective amount of the salt in Claims 1 or 4, in combination with one or more pharmaceutically acceptable carriers; Claims 19 to 22 are process and use claims; Claims 23 to 26 are omnibus claims.

6. This is the language of Claim 1:

"a dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-yl]-1-2(2,4,5-trifluorophenyl)butan-2-amine of structural formula l:



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The Parties' Evidence

7. The Opponent submitted on its behalf: an expert opinion of Prof. Abu Serajuddin (hereinafter: "**Serajuddin 1**"), an expert opinion of Dr. Leonard J. Chyall (hereinafter: "**Chyall**") and the affidavit of Mr. Darryl W. Hendricks.

8. The Applicant submitted on its behalf: an expert opinion on behalf of Prof. Jerry L. Atwood (hereinafter: "**Atwood**"), an affidavit of Dr. Robert M. Wenslow and an affidavit of Mr. Robert Di Vincenzo.

9. The Opponent submitted evidence in reply by way of an additional expert opinion of Prof. Serajuddin (hereinafter: "**Serajuddin 2**"), and an additional expert opinion of Dr. Chyall.

10. After the main round of evidence, both parties filed additional evidence, on which I shall elaborate below. I note, however, that on behalf of the Applicant, these were the affidavits of Prof. Atwood (dated August 26, 2012; March 20, 2013; September 13, 2013), which will hereinafter be referred to as "**Atwood 1**"; "**Atwood 2**"; and "**Atwood 3**", respectively. On behalf of the Opponent these were the affidavits of Dr. Chyall (dated January 24, 2013; and February 19, 2013), which will be hereinafter referred to as "**Chyall 1**" and "**Chyall 2**", respectively.

The Uncontested Facts

11. International Publication WO 03/004498 (hereinafter: "**Publication '498**") discloses a Markush formula which includes a large number of compounds and exemplifies 33 of them. Example 7 of Publication '498 describes the hydrochloride salt of sitagliptin.

12. Publication '498 also includes a list of preferred acids for the formation of salts of the compounds (p. 10 of the Publication). Among these acids is also the phosphoric acid which forms the phosphate salt. The dihydrogen phosphate salt of sitagliptin, which is claimed in the Patent Application that is before me, will hereinafter be referred to as the "**DHP salt**".

13. The DHP salt is a salt consisting of one molecule of sitagliptin and one molecule of phosphoric acid in a ratio of 1:1, and it is formed by the transfer of the first of three protons of the phosphoric acid to sitagliptin.

Novelty

14. According to the Opponent, the Applicant itself proposed to prepare the DHP salt before the Priority Date as transpires from Publication '498, by indicating the phosphoric acid as one of eight preferred acids in that publication. According to the Opponent, the question of novelty should be examined in accordance with the infringement test. In other words, it is the Opponent's position that if performing the stated in Publication '498 constitutes an infringement of the Patent Application, then the invention claimed in the Patent Application lacks novelty. The Opponent further argues in this context that this test holds even when the previous publication does not explicitly exemplify the invention, but performing the instructions in the prior art inevitably leads to the invention.

15. In the present case, the Opponent argues that an person of ordinary skill in the art who would react the active ingredient sitagliptin with phosphoric acid to form a salt as proposed in '498 would necessarily obtain the DHP salt as the only stable phosphate salt. Therefore, the Opponent holds that the DHP salt was disclosed in that publication in a manner that takes away novelty from the Patent Application. The Applicant, on the other hand, holds that such activity could result in additional products, such that it was not possible to expect the resulting product prior to performing experiments that test it.

16. In other words, the question being asked here is whether it is sufficient that a compound and an acid that are included in a previous application as one of the options therein negate novelty from a patent application that claims that specific salt.

17. Publication '498 teaches compounds that are included in a Markush formula and processes for their preparation. As is well known, the use of a Markush formula allows the patentee to obtain certain protection over the variety of chemical compounds that are included in the formula, as well as over the processes of their preparation, if these are patentable in accordance with the terms prescribed in the Law.

18. In order to negate novelty from an invention, it must be shown that there is a single prior publication that fully includes the invention's components in a manner that enables a person of ordinary skill in the art to carry out the invention (CA 345/87 *Hughes Aircraft Company v. State of Israel*, PD 44(4), 45, 102-105 (1990)) (hereinafter: "**Hughes**"). Therefore, when a prior publication expressly claims a substance, it will clearly negate novelty from a later application seeking protection over the same substance:

> "**A specific disclosure of a substance invalidates a claim to the substance, regardless of question of advantage.**"
> (Blanco White, 4th edition, pp. 4-110)

19. However, when a prior publication does not describe a known compound, but rather the compound in its free base form, its manner of preparation and its preferred salts, the question arises whether it can negate novelty from a later application that includes one specific compound from among all the possible compounds that exist in it.

20. In the decision regarding opposition to patent application 55660 (15.1.84), it was stated that: "**For a chemist, a compound is not a known compound until it has actually been prepared and identified by one of its properties or characteristics**."

21. This question was discussed again, albeit in *obiter dictum*, in CA 8802/06 *Unipharm Ltd. v. SmithKline Beecham Plc* (published in Nevo, 05-18-2011) (hereinafter: "**SmithKline**"). The court held that in order to recognize the patentability of a product which is a component of a group described in a prior patent, it must be shown that the product is new and has an inventive step, as follows:

> "**Thus, for example, the novelty requirement defined in section 4 of the Patents Law requires examining whether a property discovered in a component or components from a group described in a prior patent was disclosed and known; the inventive step requirement set forth in Section 5 of the Patents**

> **Law requires examining whether a new property discovered in a selected component, for which a new patent is being sought, is a property that embodies a substantial advantage that may constitute an appropriate consideration for granting a monopoly to the inventor**."

22. In other words, according to this ruling, in order to determine that a component was already described in a prior publication, such component need not be expressly exemplified; it is sufficient that it is described as part of a group for the question of novelty to arise in respect of it.

23. This was adopted in the work directives of the Patents Authority (see Section 6.5 of Appendix F, Edition 4, Work Directive F/23.1), where it is stated:

> **"If the publication that discloses the broad group does not include examples that describe the members of the narrow group, and the specification of the application under consideration does not describe a substantial and unexpected advantage of the entire claimed group, the Examiner must indicate a deficiency in regard to Sections 4 and 5 of the Law, based on the publication that describes the broad group to which the claimed group of members belongs."**

24. Although this section of the Work Directives was incorporated into them after the time this Opposition was heard, it is based on the judgment of the Supreme Court in the SmithKline case, published in May 2011.

25. On this question, the British approach is different, following the European Directive and the case law of the European Union. In the case of *Dr Reddy's Laboratories Ltd v Eli Lilly & Co* [2009] EWCA 1362, it was determined that for a prior publication to negate the novelty of a compound, it must describe the compound individually ("individualized description"). Sometimes, selecting the same compound from among all the compounds that are included in the Markush formula is nothing more than finding a needle in a haystack. Therefore, the Markush formula will not preclude novelty from a single compound included in it:

> "**The contention amounts to this: that every chemical class disclosure discloses each and every member of the class. It would, it seems, even apply if the formula had simply been written down without any suggested utility.**
>
> **I reject the contention for two reasons: firstly as a matter of a priori reasoning and secondly because it is inconsistent with settled EPO Board of Appeal case law.**

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