חוק הפטנטים, תשכ"ז-1967

בענין: **בקשה לרישום פטנט 172563**

ובענין: **טבע תעשיות פרמצבטיות בע"מ**

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המתנגדת

- נ ג ד -

MERCK & CO., INC., U.S.A.

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המבקשת

ראיות בתשובה מטעם המתנגדת -

חוות דעת Dr. Leonard J. Chyall

SECOND DECLARATION OF LEONARD J. CHYALL, PH.D.

I, the undersigned, **Dr. Leonard J. Chyall**, U.S. Passport No. 432624896, with a business address of Chyall Pharmaceutical Consulting LLC, 3000 Kent Avenue, Suite D1-105, West Lafayette, Indiana 47906, USA, having been warned that I must state the truth and that I shall be liable to the penalties prescribed by law should I fail to do so, hereby declare in writing as follows:

1. I am the same Leonard J. Chyall who submitted a declaration dated August 3, 2010 (the "First Declaration"), in support of the position of Teva Pharmaceutical Industries Ltd. ("Teva") in the proceedings before the Honorable Registrar of Patents regarding Israel Patent Application No. 172563 ("the Patent Application"), filed by Merck & Co. Inc., U.S.A. ("the Applicant").

2. This declaration was prepared in response to the declarations of Prof. Jerry L. Atwood, Dr. Robert M. Wenslow and Mr. Robert Di Vincenzo, submitted on behalf of Merck on June 1, 2011.

3. The fact that I have not commented on any particular point in the Declarations of Prof. Atwood, Dr. Wenslow or Mr. Di Vincenzo should not be taken to imply that I accept or agree with that point. There is nothing in these declarations that causes me to change the views that I expressed in my First Declaration.

I. PROF. ATWOOD'S ASSERTION THAT ONE COULD PREPARE SALTS OTHER THAN SITAGLIPTIN DIHYDROGENPHOSPHATE IS NOT CREDIBLE

4. Prof. Atwood performed experiments to demonstrate that salts of sitagliptin and phosphoric acid other than a sitagliptin dihydrogenphosphate salt (a 1:1

salt)[1] could be prepared. As explained below, it is my opinion that Prof. Atwood's experiments used poor experimental techniques and did not demonstrate the preparation of salts other than the reasonably expected sitagliptin dihydrogenphosphate salt. Prof. Atwood's poor experimental techniques defeat his argument that one can prepare salts of sitagliptin and phosphoric acid other than a 1:1 salt. Indeed, in one instance Prof. Atwood's poor experimental techniques led him to conclude that he had prepared a bis(sitagliptin) phosphoric acid salt (a 2:1 salt), when X-Ray Powder Diffraction ("XRPD") analysis of the reaction product proves that Prof. Atwood actually prepared the reasonably expected sitagliptin dihydrogenphosphate salt.

A. Prof. Atwood Used Poor Experimental Techniques

5. All of Prof. Atwood's experimental protocols had significant flaws, including use of irregularly high reactant concentrations and failure to filter and wash reaction products. These significant protocol flaws render Prof. Atwood's experimental conclusions unreliable and without scientific credibility.

6. **Irregularly High Reactant Concentrations:** Prof. Atwood's experiments employed concentrations of sitagliptin and phosphoric acid that were so high that they caused his reaction mixtures to solidify. It is highly irregular and improper to conduct chemical reactions at concentrations that cause the entire reaction mixture to solidify. An organic chemistry reaction, such as the addition of an acid to an organic base, should take place under homogenous (*i.e.*, uniform) conditions. Conducting the reaction with enough solvent to ensure adequate mixing throughout the experiment facilitates these conditions. One cannot ensure adequate mixing and homogeneous

[1] A sitagliptin dihydrogenphosphate salt is a salt comprising one molecule of sitagliptin per one molecule of phosphoric acid.

conditions if a reaction is conducted with too little solvent and the reaction mixture solidifies during the course of the reaction. The resulting inadequate mixing may lead to incomplete chemical reactions and may also lead to an increased formation of unwanted byproducts. For this reason, proper experimental technique would have entailed the use of enough solvent to suspend in solution any solids that formed from the chemical reaction. In my opinion, Prof. Atwood's use of too little solvent likely resulted in elevated levels of impurities, such as unreacted starting materials and/or reaction by-products, in the solid products that he obtained.

7. **Failure To Filter And Wash:** Filtration (with washing) is routinely used to separate reaction products from unreacted starting materials, impurities, and byproducts. Furthermore, such steps are essential if one seeks to use elemental analysis to determine the identity of the product. In his experiments, Prof. Atwood failed to filter and/or wash the solid reaction products that he recovered to remove such unreacted starting materials, impurities and byproducts.

8. In my opinion, even if Prof. Atwood had used the best possible protocols to conduct his experiments, the reaction products that he recovered would have required filtering and/or washing to remove unreacted starting materials, impurities and byproducts. Prof. Atwood, moreover, did not use the best possible protocols. As explained above, he used too little solvent, which likely resulted in the presence of elevated levels of unreacted starting materials, impurities and byproducts. The presence of such elevated levels of unreacted starting materials, impurities and byproducts increases the negative impact of Prof. Atwood's failure to filter and wash the reaction products that he recovered.

9. Rather than use filtration (and washing) to isolate and purify his solid reaction products, Prof. Atwood used vacuum drying to isolate solids from his reaction mixture. When vacuum drying is used to remove solvent from a reaction mixture, only the volatile materials are removed and the non-volatile materials are left behind in the product. The consequence of this drying protocol is that to the extent they are not volatile, unreacted starting materials, impurities and by-products will remain in the solid product after vacuum drying.

10. Sitagliptin and phosphoric acid are not volatile. Accordingly, any unreacted sitagliptin or phosphoric acid in Prof. Atwood's experiments would have ended up in the solid product that Prof. Atwood recovered after vacuum drying.

11. The absence of a filtration/washing step in Prof. Atwood's experiments virtually guaranteed that the solids that Prof. Atwood recovered at the end of his experiments contained the same ratio of sitagliptin to phosphoric acid as the starting materials, regardless of what type of salt (if any) formed. This is because Prof. Atwood's recovered solids would contain virtually all of the sitagliptin and phosphoric acid as either unreacted starting material or as a solid sitagliptin/phosphoric acid salt (*i.e.*, the reaction product), regardless of the stoichiometry of that salt.

B. Prof. Atwood's Identification Of The Products Of His Experiments Lacks Scientific Credibility

12. Prof. Atwood used a number of analytical techniques to analyze the products of his experiments and to determine whether he prepared a salt other than sitagliptin dihydrogenphosphate. The techniques that Prof. Atwood used, and the results he obtained, prove in one instance that Prof. Atwood obtained a sitagliptin

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