UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC

Petitioner

v.

CIPLA LIMITED

Patent Owner

Case No. IPR2017-00807

U.S. Patent No. 8,168,620

DECLARATION OF ALEXANDER DOMINIC D'ADDIO, Ph.D.

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Patent Trial and Appeal Board
U.S. Patent and Trademark Office
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Alexandria, VA 22313-1450

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I, Alexander Dominic D'Addio, declare that:

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

I. Introduction

2. In connection with this *inter partes* review proceeding, I have been asked by Cipla Ltd. ("Cipla") to explain the pharmaceutical development of Dymista®, Meda Pharmaceutical Inc.'s ("Meda") azelastine-fluticasone combination nasal spray. During the course of Dymista®'s development, Meda and its predecessor MedPointe Pharmaceuticals[1] failed to formulate and develop a nasal spray containing a single formulation of azelastine and fluticasone, and subsequently licensed the application that became U.S. Patent No. 8,168,620 ("the '620 patent") from Cipla Ltd.

3. I am being compensated for my time in connection with this *inter partes* review matter at a rate of $400 per hour, and my compensation does not depend upon the ultimate outcome of this case. I will also be compensated for any reasonable expenses, including travel costs.

4. This declaration is based on my own personal knowledge of Meda's research and development of the allergy treatment Dymista®.

5. For this declaration, I rely on the following documents:

Cipla's Exhibit #[2]	***Description***
2004	Alexander Dominic D'Addio, Ph.D. *Curriculum Vitae*

[1]In 2007, Meda acquired MedPointe Pharmaceuticals. I will refer to both companies as "Meda."

[2] Throughout this declaration, I will refer to these exhibits as "[Exhibit Number], [paragraph/page number(s)]."

2049	2006 Cipla-Meda License Agreement with Quality Agreement (PTX1016)
2054	MedPointe Making Medicine Better: Astelin® Day Life CyclePlan, November 1, 2002 (PTX1005)
2055	MedPointe Product & Process Development Program Priorities and Issues - September 9, 2002 (PTX0143)
2056	Astelin Nasal Spray Life Cycle Management Projects (Preliminary Plan) (PTX1006)
2057	2006.02.06 Email from Paul Edick to Dennis Fuge re: Pfeiffer Bi Dose Nasal Spray System (PTX0149)
2058	2006.03.21 Email and attachment from Kalidas Kale to Alex D'Addio re: Astelin – Flonase Combination Product Feasibility Assessment Plan (PTX0151)
2059	Dang, Phuong Grace, *et al.* U.S. Patent No. 8,071,073 (Filed November 22, 2005; Issued December 6, 2011)
2060	Dang, Phuong Grace, *et al.* U.S. Patent No. 8,518,919 (Filed November 10, 2011; Issued August 27, 2013)
2061	MedPointe Laboratory Notebook No. 1044 - Excerpts (PTX0142)
2120	MedPointe Product & Process Development, Program Priorities and Issues - November 18, 2002, "Commercial Product Technical Support" (PTX0144)
2121	2006.02.06 Email from Richard Spivey to Alex D'Addio re: Pfeiffer Bi Dose Nasal Spray System (PTX0150)
2122	2003.11.11 Email and attachment from Mary Lehr to Gul Balwani (PTX0255)

II. Background – Education, Expertise and Responsibility

6. I obtained my bachelor's degree in chemistry from Kean University in 1975. In 1983, I received my Ph.D. in analytical chemistry from Seton Hall University.

7. For 26 years, I was involved in the research and development of allergy-related products for Meda and its predecessors, MedPointe Pharmaceuticals and Carter-Wallace. Until February 2017, I was the Vice President of Scientific Affairs and Medical Communications at

Meda. I first joined Carter-Wallace as a laboratory supervisor in 1990. At Carter-Wallace, I was promoted to department head in 1993 and eventually became a director in 1997. After MedPointe Pharmaceuticals acquired the Wallace Laboratories division of Carter-Wallace in 2001, I was appointed Vice President of Product and Process Development, a position that I held until 2010. In that position, I supervised the research and development of new drug products for MedPointe and for Meda after its 2007 acquisition of MedPointe.

8. I was involved in the research and development of Meda's azelastine hydrochloride nasal sprays, Astelin® and Astepro®. In October 2002, Meda began to investigate an azelastine and steroid nasal spray combination project under my direction. I was involved in all aspects of research, clinical development, Food and Drug Administration ("FDA") approval, launch, and post-approval support of the product that eventually became Dymista®. My duties included overseeing the scientific effort to determine the feasibility of developing a combination nasal spray.

9. As Vice President of Product and Process Development, I oversaw Meda's Product & Process Development (PPD) group. From within the PPD group, the Formulation Development (FD) group was responsible for the research and development of potential new drugs, as well as the support of current drug products in Meda's portfolio. The FD group included Dr. Kalidas Kale, Mr. Gul Balwani, and Mr. John D'Aconti, among others. In 2002, Mr. Gul Balwani was appointed lead formulator of the group. My CV appears at CIP2004.

III. Product Journey

10. Throughout the 1990s, Meda was working to develop an azelastine hydrochloride ("azelastine") nasal spray formulation for the treatment of symptoms of allergic rhinitis. During that time, Meda had significant experience with formulating azelastine. In fact, by 2002 Meda

had over a decade of experience formulating azelastine into nasal spray formulations. By 1997, Meda received FDA-approval for an intranasal azelastine HCl product marketed as Astelin®.

11. The PPD group maintained a weekly "Program Priorities & Issues" chart that catalogued the status of all the drugs currently under development in Meda's portfolio in order to keep track of each drug's development timeline. In 2002, Meda was considering the product lifecycle strategies it would undertake for its Astelin® product. The three options being considered were: (1) making an Astelin®/steroid combination, (2) making a new Astelin® formulation that masked the bitter taste issues associated with azelastine, and (3) developing a new azelastine formulation with improved taste and dosing profiles. CIP2054, 10. By September 2002, the PPD group had started analyzing the first option: an Astelin®/steroid combination product. CIP2055, 1. The PPD group added the task "New Nasal Solution Product, Combination of Azelastine HCl and an Approved Steroid" to its weekly "Program Priorities & Issues" chart. CIP2055, 1. At that point, Meda had not selected any particular steroid allergy treatment to use in the proposed combination formulation.

12. By October/November of 2002, the PPD group had assessed the feasibility of an azelastine/steroid combination product. The PPD group viewed the technical aspects of developing an azelastine/steroid combination as "difficult" and considered the project to have a "high degree of technical difficulty." CIP2054, 11; CIP2056, 11. This assessment was based on at least two factors.

13. First, we recognized that Astelin® is a solution formulation, where the azelastine is fully dissolved in the nasal spray vehicle, but that steroids are suspension formulations, where the steroid particles are not dissolved in the nasal spray vehicle but are instead suspended in it. CIP2054, 11; CIP2056, 11. The PPD group also conducted literature searches to see whether we

could find any guidance on how to formulate a solution formulation with a suspension formulation, but we were unable to find any. *See* CIP2055, 1.

14. Second, we recognized that azelastine is dosed two sprays/nostril twice daily, while the nasal steroids are dosed two sprays/nostril once daily or one spray/nostril twice daily. This meant that the dosing of azelastine and whichever steroid selected would have to be reconciled. For example, administering a combination formulation to deliver two sprays/nostril twice daily would result in over-administering the steroid by twice the recommended dose. And administering a combination formulation on the same frequency as a steroid (two sprays/nostril once daily or one spray/nostril twice daily) would result in administering half as much azelastine as is FDA-approved. In light of these factors, I, and the PPD group, drafted two documents (CIP2054; CIP2056) to report our findings to Meda management. We reported that the technical "feasibility" of developing an azelastine/steroid combination product was "low."

15. Additionally, the PPD group recognized that because the ultimate goal was to develop a new commercial product, any combination product would need to satisfy the FDA's "combination rule" in order to be approved. It was our understanding that the FDA's combination rule required that both agents in a combination contribute to the overall efficacy of the combination product. CIP2056, 11. Again, we reported to Meda management that the "likelihood of success" of the azelastine/steroid combination satisfying the combination rule was "low" because we did not anticipate that Meda could show that the combination was actually better than the individual components. CIP2056, 11.

16. Based on the low probability of success and the anticipated technical obstacles to developing a combination nasal spray, the project became a low priority for Meda. CIP2120, 3. Instead, the PPD group began to look into alternative ways to deliver the steroid/azelastine

combination. From late-2003 through 2006, Meda began work to identify possible dual-chamber devices that would allow azelastine and fluticasone to be stored in separate bottle chambers but could also co-administer the two actives in one spray. CIP2122, 3. By January 2006, the PPD group rejected the dual-chamber approach because we were unable to find any suitable devices. CIP2057, 1-2.

17. With the dual-chamber device no longer an option, management requested that the PPD group consider developing an azelastine/fluticasone combination formulation. Although we understood that this combination product would be technically challenging, we still greatly underestimated the difficulty associated with developing the azelastine and fluticasone combination, because we believed that it was possible to create a combination formulation through either a simple solution or suspension formulation. CIP2057, 1.

18. The FD group began a small-scale formulation effort to confirm conceptually if an existing formulation could work as the starting point for the combination development. CIP2121, 2. I asked Dr. Kalidas Kale, a Senior Scientist in Liquid Formulations for Meda with experience in nasal spray development, to draft a feasibility assessment plan for an Astelin® and Flonase® combination. Dr. Kale circulated the feasibility draft in March 2006. CIP2058, 1-3. At this time, Dr. Kale had a Ph.D. in Chemistry and 15-20 years of formulation experience, and he devised three different "Combination Product Feasibility Assessment" plans. CIP2058, 2-3. These plans explored various mixtures of existing solution and suspension formulations that could potentially lead to a suitable azelastine/fluticasone combination.

19. Plan A outlined an experiment to test whether azelastine could be soluble in the Flonase® suspension. CIP2058, 2. Plan B proposed to identify a water soluble steroid compatible

with an azelastine hydrochloride solution. CIP2058, 3. Plan C proposed testing various solubility enhancement technologies to increase the solubility of fluticasone propionate. CIP2058, 3.

20. We moved forward with Plan A first, which we believed had the greatest chance of success. Under Plan A, the first step was to determine whether azelastine could dissolve in the Flonase® nasal spray formulation after the fluticasone particles had been removed. CIP2058, 2. If azelastine was soluble in the Flonase® nasal spray formulation, we would have next tried to dissolve azelastine directly into commercial Flonase®. CIP2058, 2.

21. Mr. Gul Balwani, who reported to me as the Director of New Product Formulations in the PPD group, was assigned the task of attempting to formulate the combination product. Mr. Balwani had a Master's degree in Pharmacy and was an experienced formulator, having 15-20 years of formulation experience at this point. Mr. Balwani was also a named inventor on two patents relating to azelastine formulations. *See* CIP2059, 1; CIP2060, 1.

22. Beginning on April 24, 2006, Mr. John D'Aconti, an Assistant Formulation Scientist, began experiments under the direction of Mr. Balwani to create a combination nasal spray. At this time, Mr. D'Aconti had a bachelor's degree in pharmaceutical sciences and 3-4 years of formulation experience. He first conducted a screening experiment by combining Flonase®, a commercial fluticasone propionate nasal spray, with Astelin®, a commercial azelastine hydrochloride nasal spray. This experiment was designed to understand whether any gross formulation changes occurred with the combination of Flonase® and Astelin®. CIP2061, 17. The sample was sonicated for 15 minutes and then assessed by visual observation only. CIP2061, 17. No precipitation was observed. CIP2061, 17. As this was only a screening experiment, no further assessment of this sample was done. CIP2061, 17.

23. On April 25, 2006, Mr. D'Aconti attempted the first step under Plan A: dissolve azelastine into the Flonase® nasal spray vehicle. After removing the solid fluticasone particles via centrifugation, the sample of Flonase® nasal spray vehicle remained cloudy. CIP2061, 18. Viewed under a microscope, the sample appeared to be free of any solids. CIP2061, 18. The sample was filtered, and because the force required to filter this sample was more than the filter could withstand, the sample spilled and was lost. CIP2061, 18.

24. The next day, April 26, 2006, the team prepared another sample in a similar fashion. This time, the Flonase® supernatant sample was filtered. CIP2061, 18. The sample was transferred into a pre-weighted scintillation vial containing a magnetic stir rod. CIP2061, 18. An aliquot of azelastine hydrochloride equivalent to a 0.1 % concentration in the final formulation was added. CIP2061, 18. The sample was stirred overnight. CIP2061, 18. The following morning the sample was observed for clarity/solubility, and the team found that a major portion of the azelastine hydrochloride had *not* dissolved. CIP2061, 18.

25. The following day, April 27, 2006, the sample was put through alternating cycles of stirring and heating. CIP2061, 19. The sample became an opaque white. CIP2061, 19. The sample did not change after another 15 minutes of heating. CIP2061, 19. The sample was then left overnight to cool, and the following morning the team observed that a solid had in fact precipitated out of the sample. CIP2061, 19. The team determined that the sample needed further investigation through an analytical azelastine hydrochloride assay after it had been filtered. CIP2061, 19. The following day, the team filtered the samples and submitted the samples for an azelastine hydrochloride analytical assay for further investigation. CIP2061, 19.

26. Shortly thereafter, in May 2006, Meda discovered Cipla's published patent application directed to azelastine/steroid formulations, US 2006/0025391, and that Cipla was

selling a nasal spray product Duonase—a combination formulation of azelastine hydrochloride and fluticasone propionate. I asked Mr. Balwani to procure samples of Duonase from India. Given the concerns we anticipated in 2002 followed by the difficulties we encountered in 2006, I was surprised that someone had been able to successfully develop a combination nasal spray containing azelastine and fluticasone.

27. With this new information, Meda had to decide either to continue pursuing its internal development of the azelastine and fluticasone formulation or to pursue a license from Cipla to market the combination product. Meda considered a number of factors in deciding whether to enter into a license with Cipla: the most important considerations being that Cipla had already filed a patent application on the combination nasal spray and had successfully developed a formulation that it marketed in India. It was also PPD's view that our attempts to develop an azelastine/fluticasone combination formulation had failed because none of our attempts resulted in a viable product. And given the difficulties we encountered at only the initial stages of the azelastine/fluticasone combination formulation process, the PPD group believed that further formulation efforts were futile, especially in light of Cipla's available intellectual property.

28. In November 2006, Meda and Cipla signed the agreement to license Cipla's patents. CIP2049, 25. Together, Meda and Cipla went on to successfully develop the azelastine and fluticasone combination nasal spray that would become Dymista®. The license was very important to Meda because without it, Meda would not have been able to develop and obtain FDA approval for Dymista®.

I declare under penalty of perjury that the foregoing is true and correct, to the best of my knowledge, information, and belief.

Dated: May 26, 2017

Alexander Dominic D'Addio, Ph.D.