UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

MERCK SHARP & DOHME CORP.,
Patent Owner.

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Case IPR2020-00040
U.S. Patent 7,326,708

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**DECLARATION OF STEPHEN HOWARD CYPES**

I, Stephen Howard Cypes, hereby declare as follows:

## I. INTRODUCTION

1. I am a named inventor of subject matter claimed in U.S. Patent No. 7,326,708 ("the '708 patent"). I understand that Merck Sharp & Dohme Corp. ("Merck") is the owner and assignee of the '708 patent.

2. I understand that claim 1 of the '708 patent recites a dihydrogenphosphate ("DHP") salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4] triazolo[4,3-a]pyrazine-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, a compound also known as sitagliptin, in which the DHP counterion and the sitagliptin freebase are present in a 1:1 stoichiometric ratio. I further understand that claim 4 patent recites a crystalline monohydrate of the 1:1 DHP salt.

3. In this declaration, I provide facts based on my personal, first-hand knowledge regarding the creation and identification of the crystalline monohydrate of the 1:1 DHP salt of sitagliptin.

## II. BACKGROUND

4. I received my B.S. in chemical engineering in 2002 from Cornell University, where I also received my M.Eng. in chemical engineering and an MBA in 2003 and 2012, respectively.

5. From January 2003 to January 2004, I was a Staff Chemical Engineer in the Chemical Engineering Research & Development ("CERD") group of Merck Research Laboratories ("MRL").

6. I left Merck in January 2004 to join Symyx Technologies where I served as a Director in the Life Science Research and Business Development groups. I currently serve as Vice President, Global Workflow Sales at Unchained Labs, Symyx's corporate successor.

7. In this declaration, I have cited to several documents from Merck's archives related to the research and development of sitagliptin, including a laboratory notebook that I maintained as a Merck employee. I am familiar with Merck's practices with respect to lab notebooks at the time. In the usual and ordinary course of its business, Merck issued numbered lab notebooks to scientists for the purpose of recording their daily research activity. Each lab notebook page was numbered and individual entries typically included information regarding the project or compound for which the experiment was run. Entries in my lab notebooks were made by me at or near the time that I conducted each experiment. It was also my customary practice (and one generally shared by my colleagues) to refer to particular lab notebook numbers and pages to track samples and/or experimental procedures (*e.g.*, "NB 66839-113"). A true and correct copy of my laboratory notebook (LNB 66839) may be found in EX2125.

8. In addition to my laboratory notebook, I have cited to several of my weekly reports. These weekly reports were generated as part my duties as a scientist in CERD; at the time, scientists in CERD were required to submit weekly reports in the usual and ordinary course of Merck's business to track their research progress and experimental observations. These weekly reports were composed at or near the time of the experiments in question. True and correct copies of my weekly reports may be found in EX2126.

## III. CREATION OF THE CRYSTALLINE MONOHYDRATE OF THE 1:1 DHP SALT OF SITAGLIPTIN

9. Immediately after joining Merck, I was assigned to the project team responsible for developing an inhibitor of dipeptidyl-peptidase-IV ("DPP-IV") into an oral treatment for type 2 diabetes. At this point in the DPP-IV project, the team had selected sitagliptin as the lead compound and had spent over a year developing it, including selection of a salt form, the 1:1 DHP salt. Characterization of the 1:1 DHP salt had identified a number of anhydrous polymorphs of the compound, along with several organic solvates. However, no hydrates of the 1:1 DHP salt—much less a crystalline monohydrate—had been identified.

10. In January 2003, scientists in the DPP-IV project, including myself and others from CERD and Physical Measurements, initiated a series of experiments to identify a non-solvating solvent to crystallize the 1:1 DHP salt. The goal of our experiments was to directly crystallize a pure anhydrous crystal

form without having to desolvate an intermediate solvated crystal. *See* EX2126 (Jan. 23, 2003 Weekly Report) at 2.

11. By the end of January, the team had run several solvent experiments, with mixed results. The following table summarizes our findings as of January 30, 2003, based on the criteria I had identified as important for an appropriate solvent system. *See* EX2126 (Jan. 30, 2003 Weekly Report) at 5.

| Solvent | Form a Solvate? | Becomes Amorphous? | Free Base Soluble? | Phosphate Salt Soluble? | Degrades Product? |
|---|---|---|---|---|---|
| Water | N | N | N | Y | N |
| Methanol | Y | N | | | |
| Ethanol | Y | N | Y | N | N |
| 1-Propanol | Y | N | | | |
| 2-Propanol | Y | N | | | |
| t-Butanol | N | Y | Y | | |
| Cyclohexanol | N | Y | | | |
| Ethyl Acetate | Y | N | | | |
| Acetone | Y | N | | | |
| MIBK | N | N | Y | N | Y |
| Butyl Ether | Y | N | | | |
| THF | Y | N | Y | N | N |
| n-Hexane | N | N | N | N | |
| Cyclohexane | N | N | N | N | |
| n-Heptane | N | N | N | N | |
| Toluene | N | Y | Y | Gels | |
| Acetonitrile | Y | N | | | |
| DMF | Y | N | | | |
| DMAC | Y | N | | | |
| DMSO | N | ? | | | |
| MTBE | N | ? | | | |
| Methylene Chloride | N | ? | Y | N | |

12. On February 7, 2003, I ran a crystallization experiment using isoamyl alcohol ("IAA") and found that the resulting crystal was mixture of anhydrous Forms I and III, with some amorphous material. *See* EX2125 (LNB 66839-051) at

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