UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.
Petitioner

v.

UNITED THERAPEUTICS, INC.
Patent Owner

Patent No. 9,358,240
Issue Date: June 7, 2016
Title: TREPROSTINIL ADMINISTRATION BY INHALATION

Inter Partes Review No. 2017-01621

DECLARATION OF DR. RICHARD DALBY

I, Dr. Richard Dalby, hereby declare as follows:

1. I am a Professor in the Department of Pharmaceutical Sciences at the University of Maryland School of Pharmacy. I received my Bachelor's degree in Pharmacy with honors from the Nottingham University School of Pharmacy and my Ph.D. in Pharmaceutical Sciences from the University of Kentucky College of Pharmacy. I have over 25 years of experience working and consulting in the field of inhaled and nasal medications and devices. My *curriculum vitae* is provided as Exhibit 2022.

2. I am a paid consultant for United Therapeutics, the assignee of U.S. Patent No. 9,358,240 ("the '240 patent"), in connection with IPR2017-01621. My compensation does not depend on the content of my opinions or the disposition of this proceeding. I have been retained by United Therapeutics to provide technical expertise and my expert opinion on the '240 patent.

3. While I am neither a patent lawyer nor an expert in patent law, I have been informed of the applicable legal standards for obviousness of patent claims. I understand that the Petition brought forward by Watson Laboratories, Inc. ("Petitioner" or "Watson") challenges claims 1-9 of the '240 patent.

4. For reference, below is a list of the Exhibits that are cited herein:

Exhibit No.	Description
1001	U.S. Patent No. 9,358,240
1002	Declaration of Dr. Maureen Donovan
1003	Robert Voswinckel, et al. "Inhaled treprostinil sodium for the treatment of pulmonary hypertension" Abstract #1414, *Circulation*, 110, 17, Supplement (Oct. 2004): III-295
1005	Hossein Ardeschir Ghofrani, Robert Voswinckel, et al., "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie," Herz, 30,4 (June 2005): 296-302
1006	Opti-Neb-ir® Operating Instructions, Model ON-100/2 (2005)
1008	Venta-Neb-ir® A-I-C-I Operating Instructions, Model VN-100/4
1009	Annexes to Commission Decision C(2005)3436 of 05 September 2005: Annex III –Ventavis® Labelling and Package Leaflet
1010	U.S. Patent No. 6,606,989
1012	WO 93/00951
1014	Affidavit of Christopher Butler, June 15, 2017
1031	U.S. Patent No. 5,544,646
1163	Amendment and Reply filed in 12/591,200 (Feb. 2, 2016) (with accompanying Second Declaration of Dr. Roham T. Zamanian)
2002	*Oxford Dictionary of English*. 2nd ed. Revised. Oxford University Press, 2005 (excerpt).
2003	Newman, Stephen P. *Respiratory drug delivery: essential theory and practice*. Respiratory Drug Delivery Online, 2009 (excerpt).
2006	Declaration of Dr. Edmund Elder and Exhibits Accompanying Second Declaration of Dr. Roham Zamanian Amendment and Reply filed in 12/591,200 (Feb. 2, 2016) (Ex. 1163)
2007	Finlay, Warren H. The Mechanics of Inhaled Pharmaceutical Aerosols: an Introduction. Academic Press, 2002 (excerpt).
2008	"Mechanical Ventilation." *American Journal of Respiratory and Critical Care Medicine* 196(2):P3-4 (2017).
2022	*Curriculum vitae* of Dr. Richard Dalby

I. BACKGROUND

5. Many drugs are inhaled through the mouth. Ex. 2003, 5. Inhaled drug delivery for certain conditions minimizes the amount of drug to which the

body is exposed and results in a fast onset of drug action. *Id.* at 7. To realize these benefits a drug (or drugs) is usually incorporated into small particles or droplets to form an aerosol which is inhaled by the patient. Aerosolized drug is wasted and/or poses a secondary exposure hazard if aerosol is released into the environment (which typically occurs during exhalation).

6. Drug-containing aerosols can be created using several approaches, including the use of nebulizers. *Id.* at 11-13, 18-37. Nebulizers typically generate aerosol using the energy contained in a compressed gas (jet nebulizers) or electricity (in ultrasonic piezoelectric nebulizers) acting on a water-based (aqueous) drug solution. *Id.* The particle or droplet size and concentration of the aerosol generated is highly dependent on the design of the nebulizer. *Id.* If two solutions for inhalation are functionally identical but are aerosolized by nebulizers of different design, the quantity and quality of drug delivered to the patient is unlikely to be the same. *Id.* Conversely, if the same nebulizer is used to deliver two solutions for inhalation that are functionally identical, the quantity and quality of the drug delivered to the patient would be the same, assuming the patient inhales in an equivalent manner and there are no other variables. *Id.*

7. One variable to consider during aerosol generation and administration (including by nebulization) is sedimentation. Ex. 2007, 4-7; Ex. 2003, 16-17. Aerosols consist of small particles or droplets suspended in air. Suspended

particles or droplets fall under the influence of gravity; therefore, the concentration of small particles or droplets suspended in air is time-dependent. Ex. 2007, 4-7. In order to achieve a constant (stable) concentration of suspended particles or droplets in air, either the rate at which particles or droplets are aerosolized (for example in a nebulizer) must equal the rate at which they fall out of suspension or the particle or droplet losses due to sedimentation must be negligible. *Id.* When aerosolization terminates, sedimentation of the particles or droplets continues, causing the concentration of the suspended particles or droplets in air to fall. *Id.* Therefore, the elapsed time following the end of aerosol generation can influence the amount of aerosol available for inhalation by a patient. *Id.*

II. CLAIMS OF THE '240 PATENT

8. I have reviewed the claims of the '240 patent. Provided below for reference is the language of claim 1 of the '240 patent:

> A method of treating pulmonary hypertension comprising:
>
> administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 µg/ml of treprostinil or a pharmaceutically acceptable salt thereof
>
> with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,
>
> said pulsed ultrasonic nebulizer comprising an opto-acoustical

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