UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, Inc.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
U.S. Patent No. 10,716,793

DECLARATION OF DR. AARON WAXMAN

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I, Aaron Waxman, Ph.D., M.D., declare as follows:

1. I am a pulmonary critical physician in Boston, Massachusetts. I am Executive Director of the Center for Pulmonary and Heart Disease in the Heart and Vascular and Lung Centers, and Director of the Pulmonary Vascular Disease Program at Brigham and Women's Hospital in Boston, Massachusetts. I am board certified in Internal Medicine, Pulmonary Disease and Critical Care Medicine. I have been practicing as a pulmonary and critical care doctor for over 20 years. I am a member of the American College of Chest Physicians, The American Thoracic Society, the Pulmonary Hypertension Association, and the Pulmonary Vascular Research Institute.

2. I am an Associate Professor of Medicine at Harvard Medical School and have dual appointments in the Pulmonary Critical Care and Cardiovascular Medicine divisions at Brigham and Women's Hospital. I have previously served as an assistant professor in Medicine at the Yale University School of Medicine and Tufts University School of Medicine. I have authored or co-authored more than 150 peer-reviewed journal articles, book chapters and reviews.

3. I received my Bachelor's degree from George Washington University. I received a Ph.D. in Anatomy and Neuroscience at the Albany Medical College, and an M.D. from Yale University School of Medicine. I completed my internship and residency in Internal Medicine at Yale New Haven Hospital. I also completed

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a Fellowship in Pulmonary and Critical Care at the Yale School of Medicine. My *curriculum vitae* is provided as Exhibit 2002.

4. I am a paid consultant for United Therapeutics Corporation, the assignee of U.S. Patent No. 10,716,793 ("the '793 patent"), in connection with IPR2021-00406. My compensation does not depend on the content of my opinions or the disposition of this proceeding. I have been retained by United Therapeutics Corporation to provide technical expertise and my expert opinion on the '793 patent.

5. 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 Liquidia Technologies, Inc. ("Petitioner" or "Liquidia") challenges claims 1-8 of the '793 patent.

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

Exhibit No.	Description
EX1001	U.S. Patent No. 10,716,793 ("'793 Patent")
EX1002	Declaration of Dr. Nicholas Hill ("Hill Decl.")
EX1004	Declaration of Dr. Igor Gonda ("Gonda Decl.")
EX1006	U.S. Patent No. 6,521,212 B1 to Cloutier, et al. ("'212 patent")
EX1007	Voswinckel, R., *et al.*, Abstract 218: "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension, Journal of the European Society of Cardiology, Volume 25, Abstract Supplement (August/September 2004)
EX1008	Voswinckel, R. *et al.*, Abstract 1414: "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension," Abstracts from the 2004 Scientific Sessions of the American Heart Association, *Circulation,* 110(17 Suppl.):III-295 (October 26, 2004) ("Voswinckel JAHA")

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EX1009	Voswinckel R. *et al.*, "Clinical Observations" on "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," "Letters" Section of the *Annals of Internal Medicine*, 144(2):149-50 (January 2006) ("Voswinckel 2006")
EX1010	Ghofrani, H.A. *et al.*, Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie, 30(4) HERZ, 30(4):296–302 (June 2005) ("Ghofrani") (Foreign article and English translation attached)
EX1018	Remoludin® 2004 Label
EX2008	Hill, N., "Therapeutic Options for the Treatment of Pulmonary Hypertension," Medscape Pulmonary Medicine 9(2) (2005)
EX2009	Substantive Submission filed in 12/591,200 (Mar. 9, 2015)
EX2029	Hess D., *et al*., 2007, "A guide to aerosol delivery devices for respiratory therapists." American Association for Respiratory Care
EX2030	Dennis JH, 2002. "Standardization issues: in vitro assessment of nebulizer performance." Respir Car, 47(12):1455-1458
EX2031	Hess D., *et al.*, 1996, "Medication nebulizer performance. Effects of diluent volume, nebulizer flow, and nebulizer brand." Chest, 110(2):498-505
EX2032	Rubin BK *et al.*, 2008 Treatment Delivery Systems (in Clinical Asthma) https://www.sciencedirect.com/topics/medicine-and-dentistry/nebulizer
EX2033	Gardenhire, D.S., *et al.*, 2017, A Guide to Aerosol Delivery Devices for Respiratory Therapists (4th Ed.) American Association for Respiratory Care.
EX2034	Tyvaso® Label 2021
EX2035	Bourge *et al.,* "Rapid Transition from Inhaled Iloprost to Inhaled Treprostinil in Patients with Pulmonary Arterial Hypertension", Cardiovascular Therapeutics, 31:38-44 (2013)

I. BACKGROUND

7. I have reviewed the '793 patent, and understand it to relate to the treatment of pulmonary hypertension. At the priority date of the '793 patent, as

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today, pulmonary hypertension was a poorly understood, often fatal, disease with limited treatment options. The first approved treatment for pulmonary hypertension—and the sole approved treatment for over five years—was epoprostenol, which has significant burdens and challenges to patients.

8. Epoprostenol can only be administered intravenously. Ex. 2008. Further, the half-life of this drug is just a few minutes, which means that even a short interruption in infusion could increase the risk of hemodynamic collapse and even death because of delivery complications. *Id.* Moreover, epoprostenol requires daily mixing and refrigeration, thus requiring the patient to carry a cold pack to avoid degradation at room temperature and an infusion pump in order to safely administer the drug. *Id.*

9. Later-approved intravenous and subcutaneous administration of treprostinil had some benefits over epoprostenol—for example, it is stable at room temperature and has a half-life of several hours rather than several minutes. This freed patients of having to carry ice packs to ensure the safety and efficacy of the drug. *Id.* There were still limitations to intravenous and subcutaneous delivery of treprostinil, such as intolerable site pain in some instances. EX1018, 1.

10. By the priority date of the '793 patent, clinicians had begun to explore inhalation therapies for the treatment of pulmonary hypertension. *See, e.g.,* EX1007. At that time, the only FDA-approved prostacyclin-type drug that could be given in

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