

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC.

Petitioner

v.

INO THERAPEUTICS, INC. d/b/a IKARIA, INC.

Patent Owner

DECLARATION OF DR. MAURICE BEGHETTI IN SUPPORT OF

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO.

8,293,284

I, Dr. Maurice Beghetti, declare that:

QUALIFICATIONS

1. I am the Head of the Paediatric Cardiology Unit and also am the Director of the Subspecialty Division at the University Hospital of Geneva, in Geneva, Switzerland. I hold several degrees from Genève, Université, Faculté de Médecine, including specialist degrees in paediatric cardiology. I have spent most of my professional career in Geneva, with a three-year fellowship at the Hospital

for Sick Children in Toronto, Canada with one year devoted specifically to cardiac intensive care focusing on pulmonary hypertension research.

2. I have treated patients with inhaled nitric oxide (“NO,” “inhaled NO,” or “iNO”) since at least the early 1990s, when it was first shown to be efficacious. I have both extensively studied the drug and researched its potential uses since the early 1990s. I regularly speak and lecture about treatment of pulmonary hypertension,¹ including how to treat patients with inhaled NO or how to assess the condition of a patient’s pulmonary vasculature using inhaled NO.

3. I have been and currently am a full professor at Genève, University, Faculty of Medicine, where I have taught the uses and contraindications for inhaled NO within my lectures for cardiologists, neonatologists, and intensive care specialists, as well as for nurses specialized in intensive care. I have taught these subjects at the University since 1996, first as a senior fellow, and then as an associate professor since 2001, and as a full professor since 2010.

4. I have received several awards throughout my career, including two directly related to my research on inhaled NO. In 1996, I received a clinical research award at the Hospital for Sick Children in Toronto, for my work entitled “*A comparison of inhaled nitric oxide and mild metabolic alkalosis as acute*

¹ Pulmonary hypertension is increased pressure in the pulmonary arteries—the arteries that carry blood from the heart to the lungs to pick up oxygen.

therapy for control of pulmonary hypertension following open-heart surgery.” I additionally received an award in 2000 for my research entitled “*Inhaled Iloprost versus inhaled nitric oxide in secondary pulmonary hypertension: the vasodilator capacity and cellular mechanisms.*” This award was presented by the third World Congress on Pediatric Intensive Care, held in June of 2000.

5. During the last 12 years, I have been extensively involved with numerous international, standard-setting organizations. I am a Member of the Executive Board of the Association for Paediatric PH (“pulmonary hypertension”), which has generated the TOPP Registry (for Tracking Outcomes and Practice in Paediatric PH). I am the Paediatric Member of the European Society of Cardiology (“ESC”) Working Group on Pulmonary Circulation and Right Ventricular Function. I am also the Paediatric Member of the ESC Guidelines. The guidelines are endorsed by the European Respiratory Society (ERS), the European Association for Pediatric Cardiology (AEPC) (indeed, I represent AEPC in the guidelines) and the International Society for Heart and Lung Transplantation (ISHLT). I was the Co-Chair of the Paediatric Task Force at the last World Symposium on Pulmonary Hypertension in 2013, involving representatives from numerous countries, including the United States.

6. I am a member of the editorial board of *Cardiology in the Young* and have authored numerous publications, book chapters and books on pulmonary

hypertension. I am the editor of what is currently the only book on paediatric pulmonary hypertension.

7. My research interests are focused on pulmonary hypertension and congenital heart defects in paediatric patients. I also work with colleagues and pharmaceutical companies to design pediatric pulmonary hypertension and persistent pulmonary hypertension of the newborn (“PPHN”) studies with the European Medicines Agency (“EMA”) to develop alternative treatments for patients who do not respond to treatment with inhaled NO.

8. As part of my involvement with international organizations, including the world symposia, and through consulting work where I have presented materials to the FDA as part of paediatric investigational programs for new compounds, I have been able to confirm that there are no material differences in the standards of care and clinical practice for treating patients with inhaled NO in the United States as compared to Europe. Additionally, as part of my work with the ESC guidelines, I regularly confer with practitioners in the United States, Europe, and other countries throughout the world.²

² Advisory boards involving experts in the US and Europe have been established to develop recommendations for the use of inhaled NO. *See, e.g.*, Ex. 1010, Germann, *et al.*, *Inhaled Nitric Oxide Therapy in Adults: European Expert Recommendations*, 31 *Intensive Care Med*, 1029-1041 at 1030 (2005)

Declaration of Dr. Maurice Beghetti Regarding U.S. Patent No. 8,293,284

9. A copy of my *curriculum vitae* is found in Exhibit 1003.

10. I am not an employee of Praxair Distribution, Inc.; Praxair, Inc. or any affiliated company. Rather, I have been engaged in the present matter to provide my independent analysis of the issues raised in the above-mentioned inter partes review of U.S. Patent No. 8,293,284 (“the ’284 Patent”) (Ex. 1001). I have received no compensation for this declaration beyond my normal hourly compensation of \$500/hr. for time actually spent studying the matter, and I will not receive any added compensation based on the outcome of any proceeding related to the ’284 Patent.

(“*Germann*”); *see also* Ex. 1008, Macrae, *et al.*, *Inhaled Nitric Oxide Therapy in Neonates and Children: Reaching a European Consensus*, 30 *Intensive Care Medicine*, 372-380 (2004) (“*Macrae*”); *see also* Ex. 1017, Ivy *et al.*, *Pediatric Pulmonary Hypertension*, *J Am Coll Cardiol.* 62(25_S) (2013) (“*Ivy*”). As shown by the papers resulting from these Boards, there is no major disagreement on the paediatric guidelines among practitioners with regard to the treatment approach to be used for administration of inhaled NO. There may, however, be some differences in treatment selection due to the access and reimbursement availability of different therapies in different regions of the world. However, once a particular treatment is chosen, the approach from that point on is primarily consistent worldwide.

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