UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC., APOTEX CORP., ARGENTUM PHARMACEUTICALS LLC, ACTAVIS ELIZABETH LLC, TEVA PHARMACEUTICALS USA, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC., AND SUN PHARMA GLOBAL FZE,

Petitioners,

V.

NOVARTIS AG,

Patent Owner.

Case IPR2017-00854[1]

U.S. Patent No. 9,187,405

DECLARATION OF LAWRENCE STEINMAN, M.D.

Mail Stop Patent Board
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
ALEXANDRIA, VA 22313-1450

[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.

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I, Lawrence Steinman, M.D., declare as follows:

I. Introduction and Summary

1. I am a physician with thousands of current and former multiple sclerosis patients; a researcher with over 550 publications related to neurological and immunological disorders; a professor at Stanford University; and a member of the National Academy of Sciences. I set out my full experience and qualifications below. I submit this declaration for Patent Owner Novartis AG in opposition to Petitioners' challenge to U.S. Patent No. 9,187,405.

2. The '405 Patent claims a method of dosing the drug fingolimod for patients with Relapsing-Remitting Multiple Sclerosis (RRMS). Novartis scientists Peter Hiestand and Christian Schnell discovered that doses less than half those previously thought effective could help victims suffering from the disease. Novartis applied for a patent in June 2006, and the U.S. Patent and Trademark Office (PTO) awarded claims to a 0.5 mg daily dose. Novartis sells fingolimod at that dose for RRMS under the brand-name Gilenya®.

3. Petitioners challenge the PTO's award of the Patent. Petitioners say references published before June 2006 would have made a 0.5 mg daily dose obvious to someone with skill in the field. In addition, the Patent's specification allegedly does not support parts of the claims, which Petitioners say opens the Patent to challenge as anticipated by a paper published after June 2006. In support of their

challenges, Petitioners rely on a declaration from an MS clinician, Dr. Barbara Giesser. (Ex. 1002.) The Petitions' challenges are misguided.

4. By June 2006, research had shown that fingolimod could suppress the immune system by sequestering white blood cell lymphocytes in lymphatic tissue away from the blood stream. Scientists believed this mechanism might protect against organ rejection and/or autoimmune diseases by reducing the number of circulating lymphocytes available to attack transplanted organs or the body's own tissues. One such autoimmune disease was RRMS, in which the body's immune system attacks the central nervous system (CNS).

5. Studies showed, however, that only substantial lymphocyte suppression provided any clinical benefit. Multiple papers reported that at least 80% reduction was needed to reduce organ rejection. Another paper—"Webb"(Ex. 2014)—found in an established RRMS model that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]" (*Id*. at 118.) Less suppression correlated with no clinical benefit. Human studies further showed that only daily doses of 1.0 mg or higher could suppress lymphocytes to these levels. Lower doses could not, including 0.5 mg daily. Hence, the literature in June 2006 taught that 0.5 mg daily would not be effective for RRMS.

6. Hiestand and Schnell adopted a fresh perspective to discover otherwise. They used inventive techniques with an accepted MS model to focus later in the

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