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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC.,
Patent Owners.

Case IPR2018-00892
Patent 9,326,945 B2

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–38 of U.S. Patent No. 9,326,945 B2 (Ex. 1001, "the '945 patent"). Paper 2 ("Pet."). Bristol-Myers Squibb Company and Pfizer, Inc. (collectively, "Patent Owner") filed a Preliminary Response. Paper 18 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4 (a). Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has established a reasonable likelihood that it would prevail with respect to at least one challenged claim. We thus grant Petitioner's request to institute an *inter partes* review of the challenged claims on all grounds set forth in the Petition.

A. Related Matters

The parties provide a list of numerous litigations involving the '945 patent. Pet. 1–3; Paper 7, 1–3.

B. The '945 patent

The '945 patent describes "[c]ompositions comprising crystalline apixaban particles having a D_{90} equal to or less than 89 μm, and a pharmaceutically acceptable carrier." Ex. 1001, Abstract. The compositions

can be used for the treatment and/or prophylaxis of thromboembolic disorders. *Id.*

The '945 patent discloses as follows:

> The aqueous solubility (40 μg/mL at all physiological pH) of apixaban suggests that the tablets with less than 10 mg apixaban (dose/solubility ratio=250 mL) should not demonstrate dissolution rate limited absorption since dissolution rate limitations are only expected when the dose/solubility ratio is greater than 250 mL. Based on this dose and solubility consideration, the particle size of the compound should not be critical for achieving consistent plasma profiles, according to the prediction based on the Biopharmaceutics Classification System (BCS; Amidon, G. L. et al., *Pharmaceutical Research*, 12: 413–420 (1995)). However, it was determined that formulations that were made using a wet granulation process as well as those using large particles of apixaban drug substance resulted in less than optimal exposures, which can present quality control challenges.

Id. at 1:46–60.

The '945 patent discloses as follows:

> Surprisingly and unexpectedly, it has been found that compositions for tablets comprising up to 5 mg, apixaban particles having a D_{90} (90% of the volume) less than 89 microns (μm) lead to consistent in-vivo dissolution in humans (at physiologic pH), hence, consistent exposure and consistent Factor Xa inhibition that will lead to consistency in therapeutic effect.

Id. at 1:64–2:3.

The '945 patent discloses the need for the use of a surfactant in the composition as follows:

> The invention further provides the pharmaceutical composition further comprising a surfactant from 0.25% to 2% by weight, preferably from 1% to 2% by weight. As regards the

> surfactant, it is generally used to aid in wetting of a hydrophobic drug in a tablet formulation to ensure efficient dissolution of the drug, for example, sodium lauryl sulfate, sodium stearate, polysorbate 80 and poloxamers, preferably sodium lauryl sulfate.

Id. at 2:24–31.

The '945 patent further discloses how to perform certain dissolution rate tests. *Id.* at 3:1–19; 6:24–41.

C. Illustrative Claims

Independent claims 1 and 12, reproduced below, are illustrative:

> 1. A solid pharmaceutical composition comprising a therapeutically effective amount of crystalline apixaban particles and a pharmaceutically acceptable diluent or carrier,
>
> wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 μm, and
>
> wherein at least 77 wt % of apixaban dissolves within 30 minutes in a pH 6.8 phosphate buffer containing 0.05% sodium lauryl sulfate.

> 12. A solid pharmaceutical composition comprising a therapeutically effective amount of apixaban and a pharmaceutically acceptable diluent or carrier,
>
> wherein apixaban comprises crystalline apixaban particles,
>
> wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 μm, and
>
> wherein, as measured using a USP Apparatus 2 at a paddle rotation speed of 75 rpm in 900 mL, of a dissolution medium at 37° C., at least 77 wt % of apixaban in the pharmaceutical composition dissolves within 30 minutes in the dissolution medium, and the dissolution medium is 0.05 M sodium phosphate at a pH 6.8 containing 0.05% sodium lauryl sulfate.

Ex. 1001, 9:49–57; 10:13–27.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references:

Ex. 1004, Carreiro et al., "Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict," Expert Opin. Investig. Drugs, 17(12):1937–1945 (2008) ("Carreiro").

Ex. 1007, U.S. Patent No. 6,967,208 B2 to Pinto et al., issued Nov. 22, 2005 ("Pinto").

Ex. 1008, U.S. Patent Publication No. 2006/0160841 A1 by Chenkou Wei et al., published Jul. 20, 2006 ("Wei").

Ex. 1010, Rudnic et al., "Tablet Dosage Forms," in Modern Pharmaceutics, 4th ed., G.S. Banker and C.T. Rhodes, eds., Taylor & Francis Group, Boca Raton, FL, pp. 333–359 (2002) ("Rudnic").

Ex. 1015, "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (Aug. 1997) ("FDA Dissolution Guidance").

Petitioner also relies upon the Declaration of Kinam Park, Ph.D. (Ex. 1002) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4–5):

Ground	Claims	Basis	References
1	1–38	§ 103(a)	Carreiro, Wei, and FDA Dissolution Guidance
2	1–38	§ 103(a)	Carreiro, Wei, Rudnic, and FDA Dissolution Guidance

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