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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 INDUSTIRES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC., AND SUN PHARMA GLOBAL FZE,
Petitioners,

v.

NOVARTIS A.G.,
Patent Owner.

IPR2017-00854[1]
Patent No. 9,187,405

PETITIONERS' MOTION FOR OBSERVATIONS REGARDING THE CROSS-EXAMINATION OF DR. WILLIAM JUSKO

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

Petitioners hereby submit observations on the deposition testimony of Novartis's declarant Dr. William Jusko given on April 10, 2018 (EX1064).

1. In EX1064 at 17:18-18:10, 128:11-129:25, Dr. Jusko agreed that the average weights of American women he used were "in concordance" regardless of their time-frame. This is relevant because Dr. Jusko's abandonment of his previous reliance on lower weights (*e.g.*, 70 kg) for fingolimod animal to human conversions is not justified by a change in average weight over time. EX2095 (4th Jusko Decl), ¶20; EX2024 (2nd Jusko Decl), ¶50.

2. In EX1064 at 34:7-36:8, Dr. Jusko testified that he often uses mathematics. This is relevant to Dr. Jusko's credibility based on his refusal during the deposition to confirm simple calculations or use a calculator when asked. *See e.g.*, *id.*, 72:7-90:19; EX2095, ¶¶25, 41; Paper 63, 8; EX2005 (1st Jusko Decl), ¶¶4, 21-22; EX2024, ¶¶14, 83.

3. In EX1064 at 49:10-51:4, Dr. Jusko agreed that he relied upon the FDA Guidance (EX1049) at page 10 as discussing the impact on animal scaling of steep-dose response curves for efficacy, acknowledged that the Guidance was instead "talking about steep dose-response curve for significant toxicities," and admitted that caveats regarding steep dose response for significant toxicities "would not apply for toxicity of fingolimod." *Id.*, 52:6-56:7. This is relevant to Dr. Jusko's assertion that the FDA Guidance scaling factors Dr. Benet relied upon should not

be used because fingolimod allegedly had a steep dose response curve for efficacy. EX2095, ¶16; Paper 63, 7-8; Paper 56, 15; EX1047, ¶¶59-60, 104-05.

4. In EX1064 at 58:18-60:5, Dr. Jusko testified that direct conversion of rodent to human doses, when accounting for the difference in bioavailability between species, would result in a 0.1 mg/kg dose in a mouse being about 14 mg in a human. This is relevant to Dr. Jusko's assertions that "primates would thus need an oral dose twice as large as rats to receive the same amount of drug." EX2095, ¶16. It is relevant because it demonstrates that many of Dr. Jusko's animal conversion arguments lead to human equivalent doses that are much higher than the doses already found maximally efficacious in humans in Kappos 2005. *Id.*, ¶¶20, 25, 40-41; Paper 63, 7-8; *see also*, Paper 56, 15; EX1047, ¶¶60, 70, 104-05.

5. In EX1064 at 60:6-16, Dr. Jusko agreed that the use of 70 kg human in his Fourth Declaration (EX2095, ¶20) was "a place where [he] hadn't updated the weights from 70 to 75 [kg]." This is relevant to Dr. Jusko's assertions that Dr. Benet's human equivalent dose calculations were inadequate because they did not focus exclusively on a 75 kg person. It is relevant because it indicates Dr. Jusko selected the 75 kg weight to achieve a predetermined outcome. *Id.*, ¶¶24-25, 31, 39-41; Paper 63, 7-8; EX2024, ¶50 (70 kg); EX1047, ¶¶69-70; Paper 56, 15.

6. In EX1064 at 62:6-66:14, 67:15-69:6, Dr. Jusko agreed that his clearance methodology for converting 0.1 mg/kg in rats to human doses resulted in a human

equivalent dose of 1.43 mg, that this suggested that 1.43 milligrams "should be an effective dose in humans" and would be "a reasonable effective dose in humans," that this "is not about [the] lowest effective dose," and that "one needs more information to get to a question like lowest effective dose." This is relevant to Novartis's arguments that 0.1 mg/kg in rats was "their" lowest effective dose that Kataoka tested. *Id.*, 69:15-70:12. This is relevant because Thomson (EX1005) and Kappos 2005 (EX1007) had already shown that 1.43 mg was not the lowest effective dose in humans and that the efficacy of an even lower dose, 1.25 mg, was still on the plateau of the dose-response curve. EX2095, ¶¶20, 25, 40-41; Paper 63, 7-8; *see also*, *e.g.*, Paper 56, 15; EX1047, ¶¶60, 70, 104-05.

7. In EX1064 at 72:7-16, 75:18-76:7, 86:2-21, Dr. Jusko agreed that the FDA Guidance's standard rat conversion factor of 0.162 is roughly double its standard mouse conversion factor of 0.081, that using these factors to convert from 0.1 mg/kg in mice to a human equivalent dose and from a human equivalent dose to rats results in 0.05 mg/kg in rats, and that this conversion illustrates the consequence of the standard rat conversion factor being roughly double the standard mouse conversion factor. This is relevant to Dr. Jusko's argument that he did not know why Dr. Benet did not adopt 0.1 mg/kg in rats as the lowest dose of fingolimod proven to be effective in any animal. EX2095, ¶¶3, 33-36; Paper 63, 7-8; *see also*, *e.g.*, EX2024, ¶¶68-70; EX2096, ¶¶70-74; EX2098 (Chun

Decl), ¶¶18-21; EX1047, ¶¶67-70, 102-05; Paper 56, 14-15.

8. In EX1064 at 91:21-92:13, Dr. Jusko testified that he selected a human clearance value for fingolimod for converting rat doses to human doses by first excluding an "extreme outlier" of 23.7 L/hr, then "pick[ing] a simple number that was in the middle of all those" remaining values (7.7, 7.4, 9.5, 13.4, 9.4). When Dr. Jusko was confronted with the fact that the simple arithmetic mean of these values was 9.48 L/hr, he said at first that one would do this "more precisely" by multiplying the clearance values "by the number of subjects, " but then said that he selected 10 L/hr as the coalesced value by performing a "weighted average calculation" mentally, that the value of 10 "would be the equivalent of" doing the weighted arithmetic average, and that his mental calculation of the weighted arithmetic average was his explanation for how he arrived at that number. *Id.*, 94:21-95:17, 98:4-25, 100:15-101:10. Dr. Jusko subsequently confirmed that the weighted arithmetic average was the method he described using in his declaration and that it yielded a value of 9.44 L/hr. *Id.*, 123:11-22. This is relevant to Dr. Jusko's credibility. It is also relevant to his assertion that the Board should reject Dr. Benet's use of the FDA Guidance's standard conversion factors for generating a human equivalent dose from mice and rat data because Dr. Jusko's testimony validates Dr. Benet's use of the FDA Guidance's standard conversion factors as being appropriate for fingolimod. EX2095, ¶¶22-26; Paper 63, 7-8; *see also*, *e.g.*,

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