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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

PATENT OWNER NOVARTIS'S RESPONSE TO PETITIONERS' MOTION FOR OBSERVATIONS REGARDING THE CROSS-EXAMINATION OF DR. WILLIAM JUSKO

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

Patent Owner submits this response to Petitioners' observations on the deposition testimony of Novartis's declarant Dr. William Jusko given on April 10, 2018 (Ex. 1064). At the outset, Novartis objects to the observations because they are excessively argumentative and thus not in compliance with the Patent Office Patent Trial Practice Guide. Indeed, rather than simply cite or quote to the proffered testimony, Petitioners often paraphrase it argumentatively and inaccurately. And rather than succinctly state what issue the proffered testimony is purportedly relevant to, Petitioners instead provide highly argumentative comments about what conclusion the Board should draw from the testimony. The observations should be struck in their entirety.

Response to Observation 1.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial. Dr. Jusko did not agree that "the average weight of American women he used were 'in concordance' regardless of their time frame." Rather, he pointed counsel to the underlying CDC documents (Exhibits 2104 and 2109), which do not speak to whether average weights changed from the 1990s to 2006. (Exhibit 1064 at 17:24–18:10.) Moreover, Dr. Jusko used 70 kg weights only in two places—first when he was describing a reference that used that weight for a different purpose (Ex. 2024 ¶ 50 (describing Budde 2002)), and second when using a hypothetical calculation merely to illustrate that linear scaling based on weight over-estimates

doses (Ex. 2095 ¶ 20). Dr. Jusko never adopted 70 kg as the proper weight to use when performing dose scaling for an RRMS drug in humans. After consultation with MS expert Dr. Steinman, Dr. Jusko used 75 kg for that purpose. (Ex. 2108 ¶ 3.)

Response to Observation 2.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial. Dr. Jusko explained that he was uncomfortable using a new calculator; would accept counsel's calculations unless he saw an error; and reserved the option of using a calculator later in the deposition. (Ex. 1064 at 88:25–89:9; *id.* at 150:9–18; *id.* at 153:17–154:23; *id.* at 156:16–157:19.)

Response to Observation 3.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial. Dr. Jusko's Fourth Declaration identifies a drug's steep dose response as a "confounding factor" in scaling from animal to human doses (Ex. 2095 ¶ 16), and none of the statements in this Observation are inconsistent with that point. The entire FDA Guidance is focused on identifying a safe (non-toxic) first-in-human dose. (*Id*. ¶¶ 5–6.) The FDA Guidance identifies a number of confounding factors that can undermine that methodology, and Dr. Jusko shows that those factors existed for fingolimod. (*Id*. ¶ 16.)

Response to Observation 4.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial. To start, Dr. Jusko provided extensive caveats in his testimony that this Observation omits. Moreover, Dr. Jusko testified repeatedly that counsel's human-to-rat conversion made no sense and would never be done by a real person of skill. (Ex. 1064 at 83:10–94:5; *id.* at 86:2–13.) Moreover, that projected animal-to-human doses might be higher than what had already been shown effective in humans proves Dr. Jusko's point: A person of skill would know that animal-to-human dose projection is inherently uncertain and would never be used when human PK/PD data and animal PD benchmarks already existed. (Ex. 2095 ¶¶ 5–18.) Counsel never asked Dr. Jusko about that conclusion in his Fourth Declaration.

Response to Observation 5.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial for the reasons given above in response to Observation 1. Dr. Jusko never used 70 kg to perform animal-to-human scaling for an RRMS drug.

Response to Observation 6.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial, for the reasons given in response to Observation 4. In addition, this Observation omits Dr. Jusko's numerous caveats about engaging in dose scaling at all, such as those in Exhibit 2095 at Paragraphs 5–18 (a person of skill would not use dose scaling when human PK/PD and animal PD data existed), and in Exhibit

1064 at 67:6–68:4 (explaining that extrapolation would depend on degree of confidence in EAE efficacy as a predictor of MS efficacy). Lastly, this Observation's assertion that "1.25 mg . . . was still on the plateau of the dose-response curve" is false, as shown in Dr. Steinman's Third Declaration (Ex. 2096 ¶ 77).

Response to Observation 7.

This observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial, for the reasons given in response to Observation 4. In addition, this Observation misrepresents Dr. Jusko's criticism of Dr. Benet, which in fact was that Dr. Benet selectively failed to consider the full range of doses that could be projected from the data in Kataoka. (Ex. 2095 ¶¶ 32–43.)

Response to Observation 8.

This observation is improper as unduly long and argumentative. In addition, this observation misrepresents Dr. Jusko's testimony, and is thus irrelevant and prejudicial. Dr. Jusko explained in his Fourth Declaration (Ex. 2095 ¶ 24) and his deposition testimony (Ex. 1064 at 97:18–98:16) that he selected a clearance value of 10 L/hr as an "appraisal" of where the values in Kahan 2003 "coalesce" based on his professional judgment, and he cautioned that simple arithmetic means would be an improper method for calculating clearance (*id*. at 122:12–123:10). If a more precise average were sought, Dr. Jusko explained that all of the data in Kahan 2003 would

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