UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG,
TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A., INC.,
SUN PHARMACEUTICAL INDUSTRIES, LTD.,
SUN PHARMA GLOBAL FZE and
AMNEAL PHARMACEUTICALS LLC
Petitioners,

v.

ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340[1]
U.S. Patent No. RE44,186

PATENT OWNER'S MOTION FOR OBSERVATIONS REGARDING THE CROSS-EXAMINATION OF DAVID P. ROTELLA

[1] Petitioner Wockhardt from IPR2016-01029, Petitioner Teva from IPR2016-01122, Petitioner Aurobindo from IPR2016-01117, and Petitioners Sun/Amneal from IPR2016-01104 have been added as Petitioners to this proceeding.

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Patent Owner AstraZeneca AB submits this Motion for Observations Regarding the Cross-Examination of David P. Rotella pursuant to the Scheduling Order (Paper No. 17) and the Joint Notice of Stipulation (Paper No. 57).

Observation #1 - In Ex. 2221 at 12:3-13:6, Dr. Rotella testified that the two DPP-4 inhibitors in the clinic at the time of the inventions of the RE'186 patent contained an *N*-linked P2 group (NVP-DPP728) or no electrophile on the P1 group (P32/98). *See* Ex. 2226. This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and Petitioners' Reply brief regarding selection of a lead compound (Ex. 1074 ¶¶ 10-16; Reply at 10-13), specifically, to the structural solutions to the known problem of intramolecular cyclization.

Observation #2 - In Ex. 2221 at 13:20-24 and 15:3-6, Dr. Rotella testified that Ashworth does not use the term "bulky," but rather says "beta branched," to describe P2 groups in Ashworth I (Ex. 1007). This testimony is relevant to assertions in Dr. Rotella's 2nd declaration regarding Ashworth I (Ex. 1074 ¶ 19), specifically, to his assertion that Ashworth I describes and teaches the advantages of "bulkier" P2 groups.

Observation #3 - In Ex. 2221 at 15:13-16:11, Dr. Rotella testified that Ex. 2261 correctly depicts Compounds 25 and 28 of Ashworth I (Ex. 1007). This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and the Reply brief regarding Compound 28 (Ex. 1074 ¶ 24; Reply at 14-15),

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specifically, to the correctness of his assertion that Ashworth I describes and teaches stability advantages of "bulkier" P2 groups, since Compound 28, despite the size of its P2 group, is "clearly less stable compared to Compound 25."

Observation #4 - In Ex. 2221 at 16:21-17:17, Dr. Rotella testified that Ex. 2223 correctly depicts the structural differences between a tertiary and quaternary β-carbon. This testimony is relevant to conclusions in Dr. Rotella's 2nd declaration regarding β-branching (Ex. 1074 ¶ 23), specifically, it demonstrates that the isoleucyl and cyclohexyl derivatives contain a tertiary β-carbon, whereas saxagliptin contains a quaternary β-carbon like the *t*-butyl derivative.

Observation #5 - In Ex. 2221 at 18:7-19:2 and 19:14-20:4, Dr. Rotella testified that Mentlein (Ex. 2096) relates to the natural substrates for DPP-4, molecules that DPP-4 cleaves, and discloses that these substrates contain tyrosine and histidine at the P2 position. This testimony is relevant to conclusions in Dr. Rotella's 2nd declaration regarding the teachings of Mentlein (Ex. 1074 ¶ 19), specifically, because he admitted that none of the prior art compounds he relied upon used tyrosine (hydroxyphenyl group) or histidine (imidazole group)—which Mentlein referred to as "bulky groups"—in the P2 position.

Observation #6 - In Ex. 2221 at 20:22-21:23, Dr. Rotella testified that Villhauer-1998 (Ex. 1008) included adamantyl in one of many hundreds of "even more preferred compounds." In Ex. 2221 at 22:3-21, Dr. Rotella also testified that

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Ex. 2263 correctly depicts the structures of and data for Examples 1, 3, 5, 8, and 12, which Villhauer-1998 identifies as its preferred agents. This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and the Reply brief regarding modifications of Compound 25 (Ex. 1074 ¶¶ 18, 20; Reply at 13-15), specifically, to whether one of ordinary skill would have selected adamantyl over the many hundreds of other even more preferred P2 groups from Villhauer-1998.

Observation #7 - In Ex. 2221 at 22:23-23:20, Dr. Rotella testified that, though Villhauer-1998's (Ex. 1008) DPP-4 inhibitors are *N*-linked, he had no opinion as to whether the P2 groups of *N*-linked DPP-4 inhibitors will occupy a different position in space than the P2 groups of *C*-linked DPP-4 inhibitors (*see* Ex. 2259). This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and the Reply brief regarding modifications of Compound 25 (Ex. 1074 ¶¶ 17-24; Reply at 13-15), specifically, to whether he did not consider if there was unpredictability or a reasonable expectation of success in moving the P2 group from a stable *N*-linked DPP-4 inhibitor to a *C*-linked DPP-4 inhibitor.

Observation #8 - In Ex. 2221 at 24:7-16, Dr. Rotella testified that, despite stability being a feature one has to pay attention to, he was not asked to provide opinions or comment on the stability of the compounds disclosed in Villhauer-

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1998 (Ex. 1008). This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and the Reply brief regarding the selection of a lead compound and modification of Compound 25 (Ex. 1074 ¶¶ 17-24; Reply at 13-15), specifically, to whether he did not consider the known solutions to stability in selecting his lead compound and to whether there was unpredictability or a reasonable expectation of success in moving the P2 group from a stable *N*-linked DPP-4 inhibitor to a *C*-linked DPP-4 inhibitor.

Observation #9 - In Ex. 2221 at 25:3-27:12, Dr. Rotella testified that he investigated *N*-linked DPP-4 inhibitors, including those with a cyano group, after the invention of saxagliptin while at Bristol-Myers Squibb ("BMS"). *See* Ex. 2260. This testimony is relevant to statements and conclusions in Dr. Rotella's 2nd declaration and the Reply brief regarding selection of a lead compound (Ex. 1074 ¶¶ 10-16; Reply at 10-13), specifically, to whether he did not consider the *N*-linked DPP-4 inhibitors in selecting his lead compound.

Observation #10 – In Ex. 2221 at 29:19-30:1, Dr. Rotella testified that both Augustyns-1997 (Ex. 2151) and Ashworth II (Ex. 2001) have data indicating that use of a 6-membered ring in a pyrrolidine or cyanopyrrolidine-based DPP-4 inhibitor substantially reduces activity. *See also* Ex. 2221 at 28:16-29:10; Exs. 2228 and 2230. In Ex. 2221 at 30:3-31:8 and 32:12-15, Dr. Rotella also testified that a 4,5-cyclopropyl-cyanopyrrolidine is named as a 6-membered ring. *See* Exs.

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