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., and SUN PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMA GLOBAL FZE and
AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ASTRAZENECA AB,
Patent Owner.

IPR2015-01340
Patent RE44,186[1]

PETITIONERS' RESPONSE TO MOTION FOR OBSERVATIONS REGARDING THE CROSS-EXAMINATION OF DAVID P. ROTELLA

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[1] Petitioner Wockhardt from IPR2016-01209, Petitioner Teva from IPR2016-01122, Petitioner Aurobindo from IPR2016-01117, and Petitioner Sun/Amneal from IPR2016-01104 have each been joined as Petitioner to this proceeding.

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Petitioners submit this Response to Patent Owner AstraZeneca AB's Motion for Observations Regarding the Cross-Examination of David P. Rotella ("Observations") pursuant to the Scheduling Order (Paper 17) and the Joint Notice of Stipulation (Paper 57).

Response to Observation #1 –Petitioners respond that Dr. Rotella only agreed that P32/98 "does not have a cyano group, that is correct." EX2221 at 13:5-6.

Response to Observation #2 –Petitioners respond that Dr. Rotella further testified that "The term bulky, is a term that a medicinal chemist in the year 2000, and the year 2016, that's a term that is commonly understood and it is sort of innately well understood. It's also a term that was used by others. For example, Mentlein in 1993 used the term bulky amino acid." EX2221 at 14:4-22.

Response to Observation #3 –Petitioners respond that the observation overlooks Dr. Rotella's testimony "that a medicinal chemist in the year 2000, and in the year 2016, and in the year 1990, would understand that there is a significant and material difference in the bulkiness of those two groups based on their structures. And I would not equate the term large with bulky because they are -- they describe two different features." EX2221 at 16:13-20.

Response to Observation #4 –Petitioners respond that Dr. Rotella further related a move from tert-butyl to adamantyl in terms of bulkiness: "And the

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difference between this molecule and an adamantyl substitute, it's like saxagliptin derivative, is simply the addition of a cyclohexane ring to each of the atoms on that tertiary-butyl group. And so the prior art tells you that by increasing steric bulk at the P2 position, that increases stability. And since one would want to increase stability of a DPP-4 inhibitor by modifying the orientation of the cyano group, by fusion of a cyclopropane ring as illustrated by Hanessian, that's the result of an experiment that, for a small set of compounds, that one could identify a preferred compound. So that would -- sorry -- that would lead one to identify a preferred compound from a small set of experiments." EX2221 at 75:15-76:20.

Response to Observation #5 – Petitioners respond that that Dr. Rotella further testified that the term "bulky" was well understood to a medicinal chemist in 2000. EX2221 at 14:3-22.

Response to Observation #6 – Petitioners respond that that Dr. Rotella explained that "even more preferred" in this context referred to Villhauer's preference. EX2221 at 21:1-2. In his direct testimony, Dr. Rotella explained that bulkiness was the basis for focusing on Villhauer's more preferred cyclohexyl and adamantyl embodiments. EX1074, ¶¶19-21.

Response to Observation #7 –Petitioners respond that Dr. Rotella further testified that the images in EX2259 "represent static pictures, they do not represent the dynamics of a molecule in solution, and so I would hesitate to draw any firm

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conclusions about what position in space the P2 groups would occupy." EX2221 at 24:1-6.

Response to Observation #8 –Petitioners respond that the observation is ill-founded because Patent Owner does not point to any stability data in Villhauer for Dr. Rotella to have overlooked. Moreover, Dr. Rotella testified that "the prior art tells you that by increasing steric bulk at the P2 position, that increases stability." EX2221 at 75:19-21.

Response to Observation #9 –Petitioners respond that Dr. Rotella based his selection of a lead compound on the prior art. EX2221 at 13:7-19, 42:19-43:11.

Response to Observation #10 –Petitioners respond that Dr. Rotella further testified that a medicinal chemist in 2000 was able to recognize that this structure includes a 5-membered ring and a 3-membered ring fused together, and that the IUPAC naming is "only nomenclature." EX2221 at 31:10-24.

Response to Observation #11 –Petitioners respond that Dr. Rotella testified that he agreed that compound 3 was identified by Ashworth as the optimal P1 group "among the set of molecules that they've evaluated" (i.e. only within Ashworth II). EX2221 at 33:3-11. Dr. Rotella further testified that the stability of Ashworth compound 25 is superior to Ashworth compound 3. *Id.* at 34:6-8, 42:19-43:11.

Response to Observation #12 –Petitioners respond that Dr. Rotella's direct

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testimony was that incorporation of sulfur into the P1 ring showed that changes in size could produce greater potency, not that all changes in ring size would do so. EX1074, ¶40.

Response to Observation #13 –Petitioners respond that Patent Owner is pointing to an example of a Novartis combination (N-linked Villhauer P2 groups and 4-cyanothiazolidine P1 groups), which was not the subject of Dr. Rotella's testimony.

Response to Observation #14 –Petitioners respond that Dr. Rotella further testified that Augustyns was limited to what Augustyns studied and specifically noted that Augustyns had not looked at bicyclic compounds. EX2221 at 47:15-21 & 49:12-20.

Response to Observation #15 –Petitioners respond that Dr. Rotella further testified that a double bond would flatten and rigidify the ring differently compared to the fusing of a cyclopropane ring as in Hanessian. EX2221 at 59:1-11.

Response to Observation #16 –Petitioners respond that Dr. Rotella testified that the failure in Hanessian was for a particular set of receptors. EX2221 at 63:1-3.

Response to Observation #17 –Petitioners respond that Dr. Rotella further testified that these compounds from Magnin represent a "routine investigation of a comparatively small set of compounds, which is what medicinal chemists do all the

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