

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
Petitioner,

v.

AVENTIS PHARMA S.A.,
Patent Owner.

Case IPR2019-00136
Patent 5,847,170

Before TINA E. HULSE, CHRISTOPHER M. KAISER, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION

Denying Petitioner's Request on Rehearing
of Decision Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.71(d)

I. INTRODUCTION

Neptune Generics, LLC (“Petitioner” or “Neptune”) requests rehearing of our decision (Paper 15, “Decision” or “Dec.”) denying institution of *inter partes* review of claims 1 and 2 of U.S. Patent No. 5,847,170 (Ex. 1001, “the ’170 patent”). Paper 16 (“Request” or “Req.”).¹ We deny the Request for the reasons explained below.

II. STANDARD OF REVIEW

In response to a request for rehearing, the panel reviews a decision whether to institute trial for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion may be found if there was an erroneous interpretation of law, a factual finding not supported by substantial evidence, or an unreasonable judgment in weighing relevant factors. 37 C.F.R. § 42.71(c); *Star Fruits S.N.C. v. U.S.*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *The Arnold Partnership v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004); *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000). “The burden of showing a decision should be modified lies with the party challenging the decision.” 37 C.F.R. § 42.71(d). Moreover, the rehearing request “must specifically identify all matters the [requesting] party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply.” *Id.*

III. ANALYSIS

As explained in the Decision, the Board denied institution of Petitioner’s *inter partes* review challenge on a discretionary basis under

¹ Petitioner also requested review of the Decision by the Precedential Opinion Panel (“POP”). Req. 1. The POP denied the request for POP review, and the original panel maintains authority over the present Request. Paper 19, 1–2.

35 U.S.C. § 325(d). *See generally*, Dec. 25–37. We determined that non-institution was appropriate based on, *inter alia*, comparisons of the art and arguments in the present Petition and an earlier petition challenging the same claims of the same patent, which petition was filed by Mylan (Ex. 2011) and for which the Board denied institution (Ex. 2020).

According to Petitioner, “the panel overlooked or misapprehended both the law of new chemical compound obviousness and the differences between Neptune’s and Mylan’s petitions.” Req. 4. That is so, Petitioner contends, because the art and arguments in the Petition are not similar, “much less substantially similar,” to the arguments presented by Mylan. *Id.* More specifically, Petitioner argues, the Board erred in its Decision in three ways: (1) in our comparison of Petitioner’s lead compound versus the lead compounds advanced by Mylan; (2) in finding the Commerçon reference and related argument cumulative to art and arguments raised in the Mylan petition; and (3) in our assessment of the similarities between the Wong and Klein references. Req. 5–15.

We have considered Petitioner’s arguments, but we do not agree that the Decision denying institution under § 325(d) was in error. We address in greater detail below.

Lead Compound

In the Decision, we agreed with Patent Owner that, although Petitioner’s challenge urged a “different” lead compound (paclitaxel versus Kant’s compound 20 or docetaxel), that distinction was superficial on the record before us. Dec. 28. As Patent Owner persuasively argued, “Neptune’s and Mylan’s lead compound analyses arrive at the same compound; paclitaxel having a C-10 methoxy group and a BOC sidechain, *i.e.*, Kant Compound 20.” Prelim. Resp. 20–21. And, as we also pointed

out, Petitioner turned to Kant for substantially the same reasons Mylan did—to show that a methoxy substitution at the core molecule’s C-10 position is capable of providing a more potent paclitaxel analog. Dec. 28; Ex. 2011, 6 (explaining that Kant teaches “compound 20, which displays the best tubulin binding properties of all analogues studied, the highest efficacy of the studied analogues having a docetaxel side chain, and higher efficacy than paclitaxel”).²

The Board did not find persuasive Petitioner’s argument that use of paclitaxel as the lead compound was sufficient to avoid discretionary denial on this record. Pet. 78; Paper 122–3. As we further explained,

Kant relates to paclitaxel and its analogues. Ex. 1010, 1–2. And Kant describes the same advanced precursor (10-DAB-III) that is used for the synthesis of paclitaxel as being used to synthesize Kant’s analogues with a C-10 substitution. *Id.* The Board [in *Mylan*], however, considered Kant and other evidence on these very points, when declining institution of trial for the Mylan Petition. Ex. 2020, 5, 7–8, 12.

Petitioner here urges that paclitaxel is a lead compound but, in much the same way as Kant, Petitioner’s modification of the art begins with 10-DAB-III, adding a side chain (with a BOC-containing group) and substituting a methoxy group at C-10. Pet. 37–40. Plus, as Patent Owner points out, Petitioner uses Kant in substantially the same way as Mylan did to rationalize such modifications. Prelim. Resp. 21; *see, e.g.*, Pet. 42–43, 46–47 (“[M]ethylation of C-10 showed a desirable increase in activity when compared to similar BOC-containing paclitaxel analogs. Indeed, Kant Table II . . .”). That Mylan may have jumped ahead to Kant’s compound 20, citing its favorable properties as a reason

² Mylan’s chosen terminology, sometimes describing Kant’s Compound 20 as C-10 methoxy docetaxel (as the compound includes a BOC sidechain like docetaxel) does not materially change our analysis of these similarities and it is undisputed that Kant, in fact, describes its compounds as being *paclitaxel* analogues. Ex. 1010.

for selecting and modifying it, while Petitioner gets to essentially the same compound in more than one step—with an arguably more thorough discussion on paclitaxel and the precursor used to make it and its analogues—does not, in our view, substantially or materially change the argument.

Dec. 30–31. The Board did not misapprehend or overlook Petitioner’s arguments concerning lead compounds.³ We addressed them, as noted above. Although Petitioner disagrees with our assessment of the similarities between the petitions on this issue, such disagreement does not persuasively demonstrate error that requires the Decision be changed.

In its Request, Petitioner contends the Board denied Mylan’s petition because it rejected Kant compound 20 as a lead compound. Req. 5–7 (“the Mylan decision . . . held that a POSA would not select Compound 20 as the lead compound”).⁴ Petitioner argues, *inter alia*, that “[n]ot a single one of the reasons the Board raised in rejecting Compound 20 as the lead applies to paclitaxel . . . and nothing in the Decision found to the contrary.” *Id.* (arguing “Mylan found that starting with Compound 20 as the lead

³ Petitioner requested, and was granted, the opportunity for additional pre-institution briefing to address Patent Owner’s arguments in favor of § 325(d) discretionary denial. *See generally* Paper 13.

⁴ It is also questionable whether Petitioner adequately addressed and developed *pre-institution* the arguments it is making now in its Request on this point. *See* 37 C.F.R. § 42.71(d). In the Request, Petitioner cites the Petition at pages 77–78, but those pages generically contend that “the Mylan petition relied upon completely different lead compounds.” Pet. 77–78; Req. 5–6. Petitioner also cites to a footnote of the pre-institution Reply (Paper 13). Req. 6–7 (citing Reply 2 n.1). That footnote is also generic, stating that “the Board denied Mylan’s petition, in significant part due to Mylan’s failure to establish Kant 20 as a lead compound.” Paper 13.

compound was not supported by the sole reference (Kant) Mylan cited in support of selecting it”).

Petitioner’s arguments do not justify a change in the Decision. First, we do not understand the *Mylan* panel to have simply rejected Kant’s compound 20 as a potential lead as Petitioner suggests. In its more complete context, the *Mylan* panel was unpersuaded a POSA had a sufficient reason for further modifying Kant’s Compound 20 so *both* the C-7 and C-10 positions would include methoxy groups to arrive at the claimed cabazitaxel. *See* Ex. 2020, 10–14. As we explained previously, the *Mylan* panel determined that Kant’s chemoselective approach to modifying the C-10 position cut against *also* modifying the C-7 moiety, whether based on alleged increases in potency, lipophilicity, or for other reasons. Dec. 22–23; Ex. 2020, 12–13. The chemoselective approaches here (in Kant and Wong (or Klein)), where either C-7 or C-10 *but not both* are changed, also cut against the simultaneous C-7 and C-10 methoxy substitutions advanced in this Petition, even supposing one starts with paclitaxel or the advanced taxane precursor 10-DAB-III (just as Kant did). *See* Dec. 29, 32, 34 (discussing overlap in the petitions’ simultaneous C-7, C-10 substitution theories).

Second, Petitioner’s argument that “not a single one” of the reasons for rejecting Mylan’s challenge based on Kant Compound 20 applies to choosing paclitaxel as a lead is not accurate. Req. 5–6. As the Board noted in the *Mylan* decision, one reason cited against further modifying Kant’s Compound 20 to have methoxy groups at C-7 and C-10 (changes that would decrease aqueous solubility) was that “a POSA would have known that docetaxel and *paclitaxel* were highly lipophilic and insoluble in water.” Ex. 2020, 13 (emphasis added). Thus, contrary to Petitioner’s argument, the

concerns raised by the *Mylan* panel apply to paclitaxel and would apply to the C-7 and C-10 modifications Petitioner proposes be made here. Indeed, as the Decision notes, Mylan and Petitioner made substantially the same argument in an effort to address the drawback of decreased aqueous solubility arising from the methoxy modifications being proposed. Dec. 23, 34 n.22.

Petitioner argues the *Mylan* decision rejected making substitutions at both C-7 and C-10 to increase lipophilicity, whereas Petitioner relies on Commerçon and best laboratory practices, not Kant alone and not a lipophilicity rationale. Req. 7–8. We addressed this in our Decision in crediting Patent Owner’s argument and explaining the overlap in the reasons offered for making modifications at both C-7 and C-10 in both petitions. *See, e.g.*, Dec. 29, 31–34 (addressing known structure-activity relationships, homologation, simplified synthesis, etc.). We are unpersuaded that removing a potential reason (increasing lipophilicity) for modifying the C-7 and C-10 positions on the taxane, materially changes matters when other reasons are the same or substantially so—particularly when both Mylan and Petitioner offered the same explanation for why increased lipophilicity arising from the proposed modifications would not be of concern. Dec. 23, 34 n.22. Nor do we agree with Petitioner’s suggestion that Mylan relied on Kant alone in its challenge. *See, e.g.*, Ex. 2011, 14 (describing creation of more potent analogs based on Kant and Klein), 26–27, 33–34 (describing “attractive” sites (especially C-7 and C-10) on taxanes that were known (in the prior art) for substitution with small molecules, and allegedly simple, more “straightforward” modifications compared to chemoselective techniques); Dec. 22–23, 31–32.

Petitioner also argues Mylan’s challenge was rejected because Mylan had improperly picked certain teachings in Klein (C-7 modifications), yet dismissed others (C-9 modifications). Req. 9. According to Petitioner, that criticism “simply does not apply” to Neptune’s challenge. *Id.* This argument, however, ignores that art cited in this Petition, including Commerçon and Klein, teaches the flexibility of modifications at C-9 (among other locations). Dec. 11, 21. And Petitioner, just as Mylan did, offered the same argument to explain why, notwithstanding the art’s recognition of C-9’s flexibility, the POSA would allegedly modify both C-7 and C-10, but not C-9. *Id.* at 33. Moreover, as we explained in our Decision, Wong’s cited compounds (which Petitioner argues support C-7 methoxy modifications) include an acetate moiety at C-10 (just as Klein’s did). Dec. 33. The presence of a C-10 acetate was cited by the *Mylan* panel too—indeed, as a further basis for concluding that the picking of methoxy groups for both C-7 and C-10 was rooted in hindsight. Ex. 2020, 16 (“We reach the same conclusion with respect to Klein’s C-10 acetyl.”). Hence, although Petitioner emphasizes what it regards as differences between its challenge and Mylan’s, we explained why we concluded that those differences did not outweigh the similarities sufficient to avoid discretionary denial. *See, e.g.*, Dec. 32–33 (discussing Wong and Klein).

Commerçon

We found persuasive Patent Owner’s argument that Commerçon was cumulative to art and arguments that were before the Board in Mylan’s petition. Dec. 28–29; 31–32. As explained in the Decision, Mylan provided a detailed discussion of specific prior art and background knowledge possessed by the POSA, which we found to provide substantially the same

information as in Commerçon and Petitioner's discussion of background art.

Dec. 31–32. We noted:

For example, the Mylan Petition addressed structure-activity relationships for taxanes, and cites abundant evidence on known modifications at various positions on the core, including “simultaneous” substitution at C-7 and C-10, as well as addition of a BOC group at C-3' on the side chain. *See, e.g.*, Ex. 2011, 21–27 (citing “Remington,” “Burger,” “Mellado,” “Grover,” “Commerçon (Ex. 1016) [Ex. 1018 here],” and “Potier (Ex. 1008) [Ex. 1005 here],” among other references); *see also, e.g.*, Ex. 2011, 23 (citing prior art disclosing that “[t]he 10-acetyl group does not affect the activity of paclitaxel or docetaxel in the reaction conditions examined . . . [t]hus **the C-10 region is an attractive side for [substitution].**”) (citing prior art disclosing that “[A] free hydroxyl group at C-7 is not required for in vitro activity **and this position is available for structural modifications.**”) (emphases added in Mylan Petition).

Dec. 32. We do not agree with Petitioner's contention that the Board erred in its analyses and conclusions on these points.

In its Request, Petitioner contends that Commerçon was not a principal reference, or even cited, in Mylan's petition. Req. 9–10. As such, Petitioner argues, the Mylan petition lacked the alleged “roadmap” provided by Commerçon's Figure 2, which reveals the “well-defined changes that would lead one directly to the claimed cabazitaxel” in light of Kant and Wong. *Id.* (“[N]o better lead compound obviousness illustration could be presented than in the prior art by *Commerçon* Fig. 2.”). And, Petitioner contends, the Board's “broad-brush” reliance on the background prior art discussed in the Mylan petition is clear error. *Id.*

We disagree. We recognized that Commerçon was not cited in the Mylan petition but, as explained above, determined that other art cited in Mylan's eleven pages detailing the background technology was similar to

and, on balance, cumulative with Commerçon’s disclosure—teaching, for example, that the C-7 and C-10 positions on taxanes were available and/or attractive sites for substitution. Dec. 31–32. Petitioner does not demonstrate persuasively why comparing, for purposes of a § 325(d) analysis, one relied-on reference that discloses potential sites for molecular substitutions to a collection of background references that provide substantially the same teaching is “error” on the record here.⁵ The POSA’s understanding is informed by all the relevant background knowledge and art, not a figure culled from one reference purporting to summarize otherwise known substitution sites. Dec. 11.

Moreover, in reaching our conclusion, we did not overlook or misunderstand Commerçon’s Figure 2 or its other teachings. Quite the opposite, the Decision provides a detailed discussion on Commerçon, and Commerçon’s Figure 2 is itself reproduced in the Decision. *Id.* at 10–12. As noted in the Decision, Commerçon relates primarily to synthesis of docetaxel and docetaxel side-chain analogs. *Id.* Indeed, insofar as Commerçon actually describes changes that should be made or investigated, Commerçon’s focus is at the C-3’ side-chain position—not individual, much less simultaneous changes to C-7 and C-10 of paclitaxel. In other words, the

⁵ Petitioner’s allegation that the Board “compounded its error” in not considering Commerçon on its own (Req. 11–12) is unavailing for similar reasons. We see no error in our comparison of Commerçon and Petitioner’s background discussion versus the art and background discussion in the Mylan Petition. As we explained, after considering the totality of the art and arguments, we concluded they were substantially the same. Dec. 30–35.

so-called “roadmap” from paclitaxel to the claimed compound is neither evident nor clear from Commerçon as Petitioner now suggests.⁶

Petitioner also argues we misapprehended or overlooked Petitioner’s reliance on Commerçon when we allegedly adopted the position that Commerçon merely disclosed that functional groups at C-7 and C-10 were available for substitution. Req. 10–11. That is not what the Board did. To the contrary, as noted above, we included Commerçon’s Figure 2 (to the extent it identifies sites other than C-7 or C-10 that are “flexible”) and the Board expressly mentioned Commerçon’s disclosure about, for example, tolerance for molecular changes at certain portions of the diterpene core (i.e., positions 7, 9, 10, and 19). Dec. 12. So too, we observed Commerçon’s teaching that BOC substitution at the 3'-nitrogen position (as in docetaxel) remains a substituent of choice. *Id.* at 10–11; *see also id.* 12–13 (noting similar teachings in Kant that paclitaxel analogues with BOC side chains resulted in potent compounds).

⁶ The Federal Circuit also recently held that Commerçon did not point to simultaneous C-7 and C-10 methoxy substitutions, tacitly rejecting Petitioner’s “roadmap” theory. As the court explained:

Commerçon disclosed that C3', C7, C9, and C10, and to a more limited extent C2', were modifiable. And as summarized above, the other references [e.g., Kant, Wong, Klein] investigated a diverse set of substitutions. [Appellant] reads this panoply of teachings as rendering obvious simultaneous C7 and C10 methoxy substitutions. But despite the apparent interest in taxane analogs, not a single reference relied on by [Appellant] made simultaneous substitutions of any kind at C7 and C10. *See Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC*, Case No. 2018-1804, slip op. at 15, 16, 18–21 (Fed. Cir. Aug. 14, 2019) (holding that the obviousness arguments were “emblematic of hindsight reasoning” and affirming the district court’s judgment that claims 1 and 2 of the ’170 had not been shown invalid).

As for Petitioner’s citation to Commerçon as disclosing that certain other positions (e.g., C-4, C-5) at the bottom of the molecule being “crucial” and, thus, not being changed, we do not agree that such disclosure results in a material difference relative to the art and arguments raised previously before the Office that is sufficient to avoid discretionary denial. Req. 11–12; Pet. 28–29. Petitioner does not cite, nor do we discern, any part of the Board’s *Mylan* decision that hinged on a concern or finding that the allegedly “crucial” portions of the molecule would be changed. The focus in *Mylan*’s petition, as here, was on the reasons for modifying the C-7 and C-10 positions (and, to a lesser extent, the reasons for not modifying C-9). But, as we explained, the flexibility, suitability, and attractiveness of those specific positions for modification was well known as evidenced by art before the *Mylan* panel and this panel.⁷ See Dec. 10–16, 30–35; Ex. 2011, 1, 5–9, 16–27; Ex. 2020, 6–10. Section 325(d) does not require the art or arguments be *identical* to what the Office previously considered. And the Board is not foreclosed from considering the art and arguments in the respective records *as a whole* when exercising discretion under § 325(d).

Petitioner’s contention that it presented non-cumulative arguments in its background section compared to *Mylan*’s petition is also unavailing. Req. 12–13; see, e.g., Dec. 33–34. What Petitioner primarily cites are *additional* rationales that *Mylan* offered (e.g., motivation to increase analog lipophilicity), which Petitioner contends it did not raise. Req. 12–13. As we discussed above, we are unpersuaded that de-emphasizing or removing a

⁷ Petitioner’s own filings also concede that art besides Commerçon, including importantly Klein, disclosed that certain positions at the bottom of the molecule, such as C-4, were “crucial.” Pet. 42 (citing Klein 276, 280).

rationale for potentially modifying the taxane molecules to arrive at the claimed cabazitaxel in the present Petition is sufficient to avoid discretionary denial under § 325(d). To the extent there are alleged “differences” in the petitions, we have addressed those above and in the Decision. Dec. 30–35. Contrary to Petitioner’s contentions, we do not agree that the manner in which we did so demonstrates “error” or an abuse of discretion. Req. 13–14.

Wong versus Klein

According to Petitioner, “[n]o reasonable examiner reviewing Klein and Wong would find these references remotely similar.” Req. 14. Petitioner alleges that Klein “discloses 9-dihydrotaxane analogs,” not “paclitaxel analogs” like Wong. *Id.* Petitioner also repeats its contention that one of the reasons cited by the Board in *Mylan* for rejecting the petition was Mylan’s selection of Klein’s favorable C-7 modification, but not Klein’s C-9 modification. *Id.* at 15.

We noted the differences in Klein and Wong in the Decision (Dec. 28–29, 31–33) and in our analysis above (*supra*, 8–9). We also pointed out what we find are the substantial similarities between the art and arguments based on Wong versus Klein, and why we concluded that exercise of discretion under § 325(d) was appropriate in light of those and other similarities. Dec. 28–29, 31–33; *supra*, 8–9). We need not repeat that analysis here.

Moreover, if Klein’s compounds are so different from paclitaxel or Wong’s compounds, as Petitioner now contends, that fails to explain why Petitioner expressly cited Klein (Pet. 44) in the Petition as evidencing a reason that the skilled artisan would not make changes at C-9 of Petitioner’s proposed, modified paclitaxel compound. Klein’s compounds are reasonably considered paclitaxel and docetaxel analogs. Indeed, its present

arguments notwithstanding, Petitioner earlier described Klein’s Table 1 as “comparing Taxol® [i.e., paclitaxel] and *its direct analog* 9-Dihydrotaxol (Klein compound 12).” Pet. 44 (emphasis added); *see also* Ex. 1016, 279 (describing preparations of 9(R)-dihydrotaxotere, a docetaxel analog). Also, the only apparent difference between the compound from Klein that Mylan relied on and the compound from Wong that Petitioner relies on is at the C-9 position. *Compare* Ex. 1016, 281 (Table III), *with* Ex. 1011, 22:46–59. Klein reduces the carbonyl (CO) at C-9 in its example, and Wong does not. *Id.*; Dec. 32–33. We explained why that difference did not avoid discretionary denial. Dec. 32–33; *supra*, 8–9.

At bottom, Petitioner disagrees with our comparison of Wong and Klein. But that disagreement does not show that we erred.

Other

In a footnote, Petitioner alleges that the Board erred in finding that related district court litigation supported non-institution. Req. 15 n.1. According to Petitioner, “this [litigation] was not an independent reason to decline institution.” *Id.* We did not, however, treat the litigation as an independent reason to exercise our discretion here. As we noted, we considered the completed district court litigation and then-pending appeal to the Federal Circuit only as an “adjunct” to our § 325(d) analysis. Dec. 35–37. We also declined to reach the issue of discretionary denial under § 314(a) and, therefore, did not “rely[] wholesale on the District Court’s order” as part of a § 314(a) analysis (e.g., applying *General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, Case IPR2016-01357, slip op. at 8–10, 16–19 (PTAB Sept. 6, 2017) (Paper 19) (precedential)) as Petitioner asserts. Req. 15 n.1. Petitioner’s allegations on these points do not demonstrate error and, thus, we decline to change the Decision.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not demonstrated that we abused our discretion in denying institution under 35 U.S.C. § 325(d). Accordingly, the Request is denied.

Outcome of Decision on Rehearing:

Claims	35 U.S.C. §	Basis	Granted	Denied
1, 2	§ 103	Wong		1, 2
1, 2	§ 103	Kant		1, 2
1, 2	§ 103	Commerçon		1, 2
2	§ 103	Bouchard		2

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