Trials@uspto.gov
571.272.7822

Paper No. 15
Filed: May 6, 2019

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 Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Neptune Generics, LLC ("Petitioner"),[1] on October 31, 2018, filed a Petition to institute *inter partes* review of claims 1 and 2 of U.S. Patent No. 5,847,170 (Ex. 1001, "the '170 patent"). Paper 1 ("Pet."). Aventis Pharma S.A. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp."). We granted (Paper 11) Petitioner's request to file a pre-institution Reply to Patent Owner's Preliminary Response to address arguments related to discretionary denial of the Petition. Paper 13.

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the Petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon considering the arguments and evidence, we determine that it is appropriate to exercise the Board's discretion to deny institution under 35 U.S.C. § 325(d). Thus, as explained further below, we do not institute an *inter partes* review of claims 1 and 2 of the '170 patent.

II. BACKGROUND

A. Related Matters

Petitioner identifies litigation related to the '170 patent including *Sanofi-Aventis US LLC v. Fresenius Kabi USA, LLC*, No. 14-7869 (D.N.J. filed Dec. 17, 2014).[2] Pet. 8. According to Petitioner, "[a]pproximately one year ago the District of New Jersey held a bench trial on validity and infringement relating to the '170 patent and certain Abbreviated New Drug

[1] Petitioner lists several entities as the real parties-in-interest. Pet. 7–8. We do not repeat that listing here.
[2] This case was consolidated for trial with several other pending cases. Ex. 1049, 1 n.1.

Applications." *Id.* at 34–36; *see also* Prelim. Resp. 11–13 (stating that the '170 patent was the subject of "a Hatch-Waxman action before the District of New Jersey involving, at its peak, 10 defendants," and ending in "an 8-day bench trial"). Petitioner further notes that the district court, at the trial's conclusion, held that the '170 patent's claims had not been shown to be obvious. Pet. 34; Ex. 1049, 29, 83.

Patent Owner states that "the district court defendants [from the litigation noted above] appealed and that appeal is now pending at the Federal Circuit." Prelim. Resp. 14. According to Patent Owner, "the district court case has been completed, and the appeal of the district court's decision upholding the '170 patent is ready for oral argument at the Federal Circuit." *Id.* at 28; *see Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc.*, No. 2018-1804 (Fed. Cir.).[3]

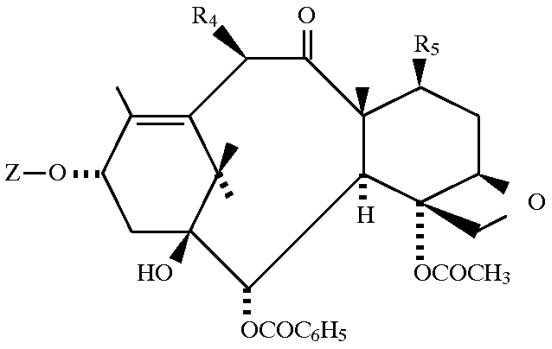
As for related matters before the Board, Petitioner identifies an earlier challenge to claims 1 and 2 of the '170 patent in *Mylan Laboratories Limited v. Aventis Pharma S.A.*, IPR2016-00627 (filed Feb. 17, 2016). Pet. 9; *see also* Ex. 2011 ("Mylan Petition"). Petitioner notes the Board's denial of institution of *inter partes* review in this earlier matter. Pet. 77–78; Ex. 2020 (Aug. 23, 2016, Decision Denying Institution); *see also* Ex. 2021 (Jan. 26, 2017, Decision Denying Petitioner's Rehearing Request).

[3] Case Number 2018-1804 at the Federal Circuit is the lead case for other related appeals (Nos. 2018-1808 and 2018-1809), and involves the appeal of several district court cases that were consolidated for discovery and/or trial. *See, e.g., Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*, No. 2018-1804, Document 68, 1–2 (Fed. Cir. filed Aug. 20, 2018). Oral argument before the Federal Circuit is scheduled for June 5, 2019. *Sanofi-Aventis*, No. 2018-1804, Document 116 (Notice of Oral Argument).

Notwithstanding the related matters above, Petitioner states that it "has never been accused of infringing the '170 patent, nor has [Petitioner] previously filed IPR petitions against any related patents." Pet. 78 n.3.

B. The '170 Patent and Background on Taxoids

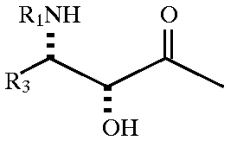
The '170 patent, which issued December 8, 1998, relates to compounds known as "taxoids." Ex. 1001, Abstract, 1:7. The '170 patent's taxoids have the following general formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):

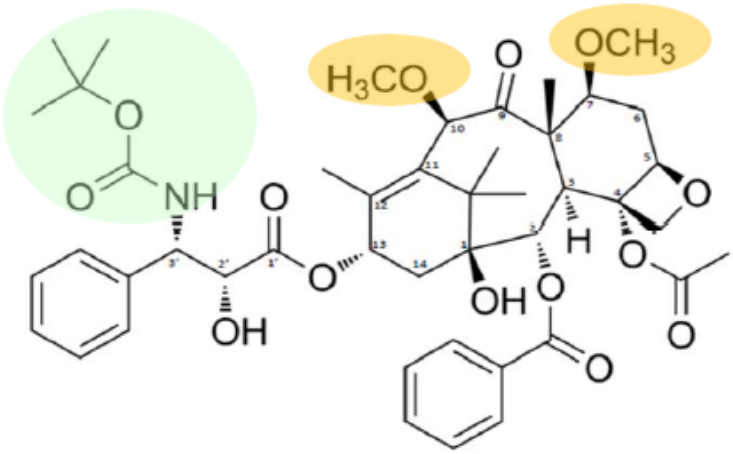


(II)

Ex. 1001, 1:7–28. The '170 patent discloses that "radicals R_4 and R_5, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms." *Id.* at 3:62–64. According to the '170 patent, "[t]he new [taxoid] products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®." *Id.* at 11:59–63 ("Such tumours comprise colon tumours which have high expression of the mdr 1 gene (multiple drug resistance gene)."). Taxol® is the trade name for the compound paclitaxel, a taxoid known in the

prior art. Ex. 1002 ¶ 71; Ex. 1009, 2; Ex. 1010, 1.[4] Taxotere® is the trade name for another known taxoid, docetaxel, a semi-synthetic analog of paclitaxel. Ex. 1009, 2; Ex. 1011, 2.

The claims of the '170 patent challenged here are directed to a specific compound known as cabazitaxel and to compositions comprising the compound. Ex. 1001, 28:57–65 (claims 1 and 2); Pet. 1; Ex. 1002 ¶ 37. The chemical name for cabazitaxel is 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenlypropionate. Ex. 1001, 28:56–60; Ex. 1002 ¶¶ 36–37. Cabazitaxel's chemical structure is shown below:

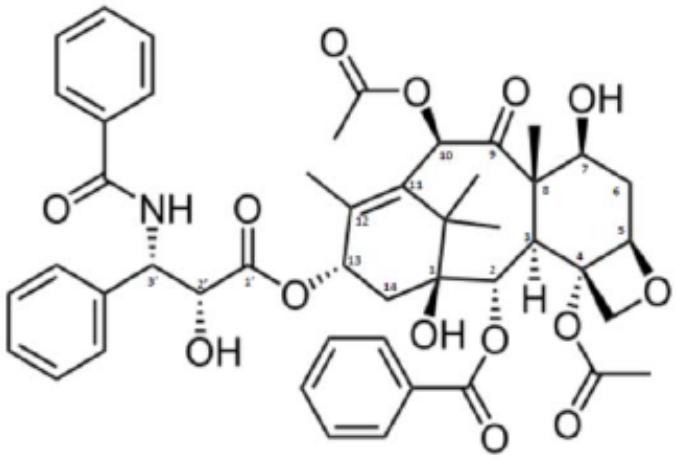


Ex. 1002 ¶ 37 (annotations added). Relevant to the challenge in this Petition, we highlight in orange the two methoxy (OCH_3) groups at the C-7 and C-10 positions (R_5 and R_4, respectively in Formula I of the '170 patent). We highlight in green the 3-tert-butoxycarbonylamino group (3'-NHBOC, which we refer to herein as a "BOC" group) at the C-3' position of the

[4] For purposes of the citations to the prior art (e.g., Exs. 1009, 1010, etc.), we refer to the page numbers provided on the exhibit copies, rather than the references' original page numbering.

compound's side chain (Formula II), the side chain being attached at C-13. *See* Prelim. Resp. 4 (showing side chain and core portions of cabazitaxel).

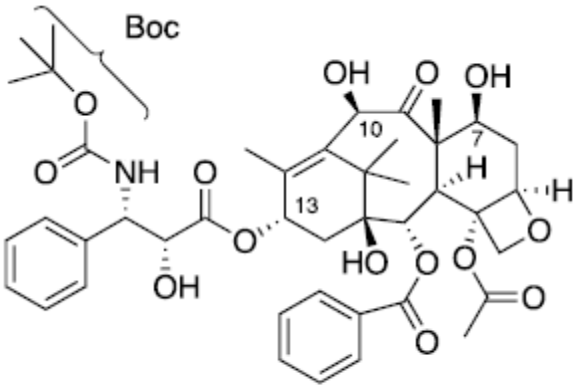
We also reproduce below the chemical structures of two known and widely-studied taxoids, Taxol®/paclitaxel and Taxotere®/docetaxel, and discuss the structural differences between those compounds and cabazitaxel.



Paclitaxel Structure

Pet. 17; Ex. 1002 ¶ 72. Paclitaxel's structure is shown above and includes, compared to cabazitaxel, different substituents at C-7, C-10, and at the C-3' position on the side chain. Paclitaxel has a benzoyl group attached to the nitrogen at C-3', not the BOC group as in cabazitaxel. Pet. 2. Paclitaxel also includes an O-acetyl/acetate (CH_3COO) group at C-10 and a hydroxyl group (OH) at C-7, not methoxy groups at those positions like cabazitaxel. *Id.*

Docetaxel, on the other hand, includes the same BOC-containing side chain as cabazitaxel, as illustrated in the chemical structure below.



N-debenzoyl-*C*-10-deacetyl-*N*-(*t*-butoxycarbonyl) Paclitaxel
(a.k.a. Docetaxel)

Ex. 1002 ¶ 98 (Decl. Fig. 8 (partial)). Docetaxel, like paclitaxel, differs from cabazitaxel's structure at the C-7 and C-10 positions. As shown above, docetaxel includes hydroxyl groups at both C-7 and C-10—not the methoxy groups at those positions as in cabazitaxel. *See* Ex. 2020, 5–6 (comparing structures for cabazitaxel, paclitaxel, and docetaxel).

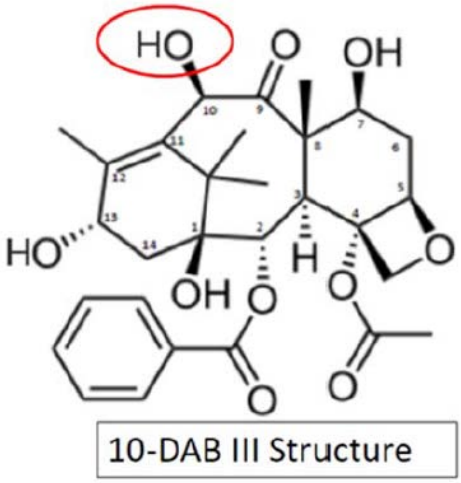
By the mid–1990s, and before the earliest putative priority date of the '170 patent, it was well-known that taxanes,[5] especially paclitaxel and docetaxel, have significant anticancer properties. Ex. 1002 ¶ 48. Those properties derive from the ability of such taxanes to stabilize microtubules and, thus, disrupt the rapid division of cancerous cells undergoing mitosis. *Id*. ¶¶ 48, 74–75; Ex. 1009, 2; Ex. 1010, 1; Ex. 1010, 2.

Paclitaxel was the first formally isolated taxane and, by the 1970s, its structure and ability to inhibit cancerous cell growth were reported in the literature. Ex. 1002 ¶¶ 71–73; Ex. 1009, 2; Ex. 1008, 2. Although paclitaxel was initially isolated from the bark of the yew tree (*Taxus brevifolia*), the extraction process produced low yields and was fatal to the tree, limiting

[5] Taxane diterpinoids (like paclitaxel, docetaxel, and cabazitaxel) are also known as taxoids. Ex. 1009, 2. We may, at times herein, use the terms taxane and taxoid interchangeably.

supply. Ex. 1002 ¶ 80; Ex. 1009, 2; Ex. 1010, 2. By the early 1990s, however, researchers had discovered that paclitaxel and docetaxel could be produced through a process that started with a naturally-occurring and abundant semi-synthetic precursor, 10-deacetyl baccatin III ("10-DAB-III"), which could be isolated from the needles of the yew tree without killing the tree. Pet. 18–19; Ex. 1002 ¶¶ 83–86, 93–96; Ex. 1009, 2–3.

The chemical structure of 10-DAB-III is shown below.



Pet. 3; Ex. 1002 ¶ 87. As illustrated in the structure above, 10-DAB-III contains the tetracyclic core of paclitaxel and docetaxel, but includes a hydroxyl group (red circle) at C-10 rather than paclitaxel's acetate group at that position. Pet. 3; Ex. 1002 ¶ 88. And, as illustrated above, 10-DAB-III lacks a side chain at C-13—either with the benzoyl group at C-3' like paclitaxel, or with the BOC group at C-3' like docetaxel. Pet. 18–19 (showing side-chain and C-10 acetate addition to 10-DAB-III to arrive at paclitaxel), 25 (showing addition of BOC-containing side-chain to 10-DAB-III to arrive at docetaxel). The '170 patent also describes processes that use 10-DAB-III as an advanced precursor for synthesizing the allegedly new taxoid compounds. *See, e.g.*, Ex. 1001, 7:23–38.

C. Challenged Claims

Petitioner challenges claims 1 and 2, which read as follows:

> 1. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenlypropionate.
>
> 2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

Ex. 1001, 28:57–65.

D. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1 and 2 are unpatentable based on the grounds in the table below. Pet. 16.

Grounds	References	Basis	Claims
1	Commerçon,[6] Kant,[7] and Wong[8]	§ 103	1 and 2
2	Commerçon, Kant, Wong, and Bouchard[9]	§ 103	1 and 2

[6] A. Commerçon et al., *Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues*, in TAXANE ANTICANCER AGENTS (Chapter 17), 233–246 (Georg, G. et al. ed., American Chemical Society Symposium Series, 1994). Ex. 1009 or "Commerçon."
[7] Joydeep Kant et al., *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol® Analogues*, 35 TETRAHEDRON LETTERS 5543 (1994). Ex. 1010 or "Kant."
[8] Wong et al., US 6,201,140 B1, issued Mar. 13, 2001. Ex. 1011 or "Wong."
[9] Bouchard et al., US 5,587,493, issued Dec. 24, 1996. Ex. 1014 or "Bouchard."

Petitioner also relies on the Declaration of John L. Wood, Ph.D. (Ex. 1002), among other evidence.

III. ANALYSIS

A. Overview of the Asserted References

We provide overviews of Commerçon, Kant, and Wong below.[10]

1. Commerçon (Ex. 1009)

Commerçon relates to synthesis of docetaxel and docetaxel side-chain analogs. Ex. 1009, 2, 12. Commerçon discloses that "[s]tructure-activity relationship studies demonstrate that biological activity is very dependent on the position and nature of substituents on the aromatic ring of 3'-modified-phenyl analogs." *Id.* at 2. Commerçon discloses that "*tert*-butoxycarbonyl [i.e., BOC] remains the substituent of choice for the 3'-nitrogen atom" and teaches that, among the new taxoids studied, "3'-*para*-fluoro-docetaxel was identified as one of the most powerful analogs of docetaxel." *Id.*; *see also id.* at 12.

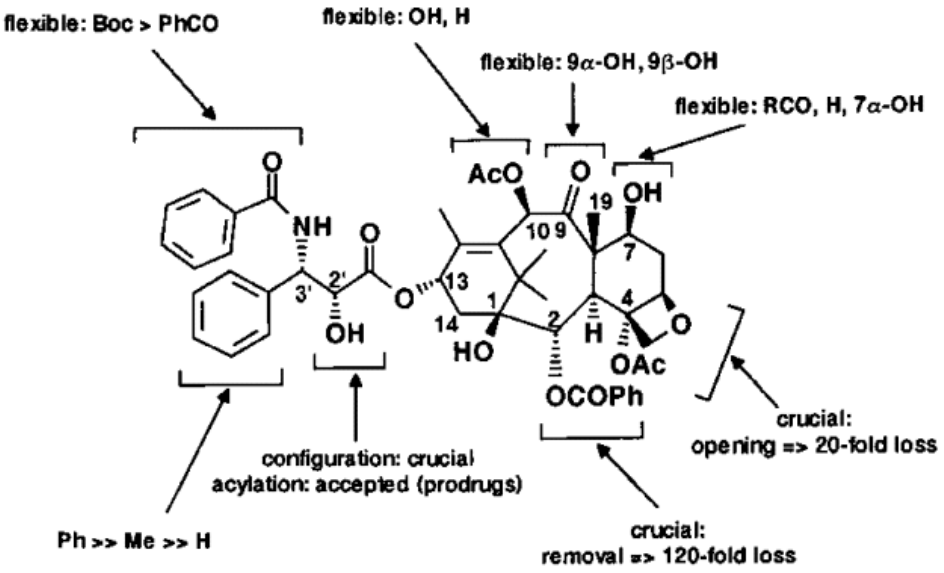
Commerçon notes that, compared to paclitaxel, docetaxel includes a BOC group instead of a benzoyl group on the C-3' nitrogen atom and includes a hydroxyl function instead of paclitaxel's acetate at the C-10 position. Ex. 1009, 3. According to Commerçon, "[t]hese structural

[10] Petitioner's reliance on Bouchard relates principally to the teaching that lipophilic taxanes may be formulated with known adjuvants or excipients. Pet. 32–33. Petitioner, for Ground 2, relies on Bouchard to address those elements added in dependent claim 2. Pet. 59–61. For Ground 1, which does include Bouchard, Petitioner challenges claim 2 over the combination of Commerçon, Kant, and Wong, and a skilled person's knowledge that formulating lipophilic taxanes (like paclitaxel) with solubility-enhancing adjuvants or excipients was a "customary" technique as described in the '170 patent and other art generally. Pet. 57–58.

modifications [on docetaxel] lead to an increase of cytotoxicity in certain experimental models," and thus, "[t]hese results suggested the possibility of further improvement by introducing, for instance, new side-chain modifications." *Id.*

Commerçon also includes Figure 2, reproduced below, as illustrating "present knowledge" related to structure-activity relationships for taxoids. *Id.* at 3 ("Structure-activity relationships of taxoids have already been reviewed . . . and our present knowledge in this area can be outlined as depicted in figure 2.") (citations omitted).

Figure 2. Modifications influencing the cytotoxicity of paclitaxel.



Id. at 4. Figure 2 indicates, *inter alia*, that the substituent at the 3' nitrogen on the side chain is "flexible" and including a BOC group provides greater cytotoxicity than a benzoyl group at that position ("Boc > PhCO"). *Id.*

According to Commerçon, other portions of the molecule are also "flexible" and can be modified without a significant effect on cytotoxicity.

Id. at 3–4. For example, Commerçon states that a "wide number of modifications can be introduced at the 7-position without significant loss of activity." *Id.* Commerçon discusses certain other known and potential modifications (e.g., at C-9, C-19, etc.) and states that "the top part of the diterpene moiety, that is positions 7, 9, 10 and 19, tolerate a wide variety of substituents," and "[t]his allows us to assume that this region of taxoids may not play a crucial role in microtubule binding or, to some extent, to cytotoxicity." *Id.* at 4.

After summarizing other known structure-activity relationship studies, Commerçon states that "[t]hese preliminary results suggested that other modifications at C-3' might further improve the antitumor efficacy." *Id.* at 5. Commerçon then reports "[Commerçon's] results regarding the stereoselective semisynthesis of docetaxel and new taxoids with either a 3'-modified-phenyl ring or a 3'-N-modified-carbamate moiety, along with their biological activity." *Id.* at 5–12.

2. Kant (Ex. 1010)

Kant relates generally to the synthesis and properties of paclitaxel analogues, having different groups at the C-10 position. Ex. 1010, 1. As explained in Kant, the authors "were interested in replacing the C-10 acetate moiety [of paclitaxel] with other functionalities." *Id.* As with the synthesis of paclitaxel, Kant discloses that "10-DAB [10-deacetyl baccatin III] was envisioned to be the ideal starting material" for synthetic and "chemoselective" manipulations at the C-10 position and the synthesis of Kant's analogues. *Id.*; *see also id.* (teaching "the side chain can always be introduced at a later stage by using a variety of published procedures").

Further to Kant's chemoselective synthesis, Kant discloses that, "with the more reactive C-7 hydroxyl protected, an opportunity was available to

selectively deprotonate the C-10 hydroxyl." *Id.* at 2. By protecting the C-7 position, Kant discloses that one can "introduce a variety of functionalities (esters, ethers, carbonates . . .) at the C-10 position of baccatin in moderate to high yields." *Id.*

Kant discloses that several "[a]ll new analogues were evaluated in tubulin polymerization[] and *in-vitro* cytotoxicity assays performed using the HCT 116 human colon carcinoma cell lines." *Id.* at 3. The results of this evaluation are reported in Kant's Table II. *Id.* (Table II (showing results for Taxol®/paclitaxel (compound 1)[11] and ten analogues)).

Among the compounds evaluated is analogue number 20 (hereafter "Kant compound 20"), which includes a methoxy group at C-10, a C-7 hydroxyl, and a BOC-containing side chain. *Id.* at 3. Kant discloses that "[a]ll new compounds displayed cytotoxic properties," but "[a]nalogues with C-10 methyl ether ([compound] 20) or methyl carbonate (22) with Taxotere™ side chain (*i.e.*, 3'-NHBOC) were found to be more cytotoxic than paclitaxel (1) or 10-acetyl taxotere (15)." *Id.* at 4. ("These compounds [20 and 22] also exhibited better tubulin binding properties."). Kant further discloses that "with the paclitaxel side chain, the corresponding C-10 modifications resulted in analogues (19 & 21) exhibiting tubulin binding similar to paclitaxel but less cytotoxic than the parent compound, with the exception of C-10 carbamate (18), which was found to be more potent than paclitaxel." *Id.* Kant concludes that, "[i]n view of our studies, it is reasonable to suggest that the functional group present at the C-10 position

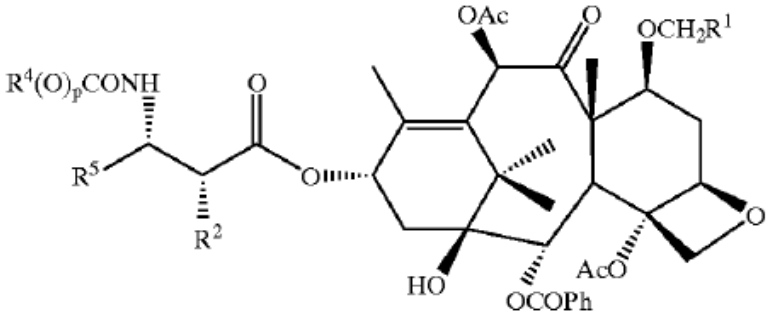
[11] Table II indicates that Taxol® includes a "Ph" (phenyl) moiety at R_1 (R_1 being attached to an oxygen, which itself is attached to C-10). Ex. 1010, 3. This is an apparent typographical error, as Taxol® has an acetyl group at R_1/C-10 as elsewhere described in Kant. *Id.* at 1–2; Ex. 1002 ¶ 179.

does modulate the antitumor activity, which is quite contrary to some of the earlier predictions." *Id.*

3. Wong (Ex. 1011)

Wong relates generally to taxane derivatives and their use as antitumor agents. Ex. 1011, Abstract. More specifically, Wong discloses "taxane derivatives having the formula (I)" as shown below.

(I)

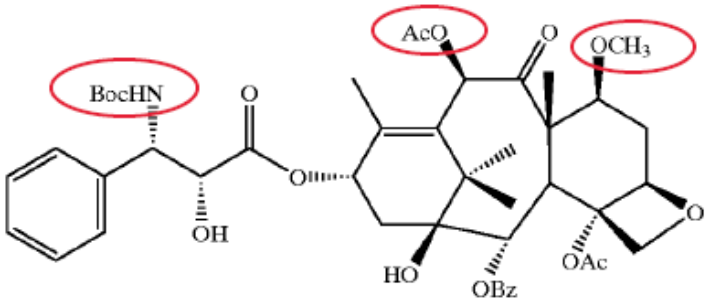


Id. at 2. Wong teaches that R_1 in formula (I) may comprise a variety of substituents such as hydrogen, a C_{1-8} alkyloxy, or C_{2-8} alkenyloxy. *Id.* When R_1 is hydrogen, a methoxy group is at the molecule's C-7 position. According to Formula (I), an acetate moiety ("OAc") is at the C-10 position.

Wong exemplifies 22 compounds of formula (I), one of which is Example 2, depicted below.

EXAMPLE 2

3'-N-Debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylpaclitaxel



Ex. 1011, 12 (annotations added). The compound depicted in Example 2 above includes a methoxy group (OCH_3) at the molecule's C-7 position. Like docetaxel, the Example 2 compound includes a BOC group attached to the nitrogen atom at the 3'-C position on the side chain. And, like paclitaxel, the Example 2 compound includes an acetate substituent (AcO) at C-10.

Wong also discloses a study on hybrid mice implanted with M109 lung carcinoma. Ex. 1011, 5–6. The mice were grouped and treated with some of the exemplary compounds via "intraperitoneal injection of various doses on days 5 and 8 post-tumor implant," and one group remained untreated as a control. *Id.* at 6. The mice were followed for daily survival. *Id.* The results, specifically median survival times, are reported in Table 1. *Id.* (Table 1, providing results for ten example compounds, including Example 2). Wong concludes that "[c]ompounds of formula (I) . . . are effective tumor inhibiting agents, and thus are useful in human and/or veterinary medicine." *Id.*

B. Person of Ordinary Skill in the Art

Petitioner proposes the following qualifications for the person of ordinary skill in the art:

> A POSA at the relevant time would possess the following qualifications: (a) a Ph.D. in organic chemistry, medicinal chemistry, or a closely related discipline, or (b) a master's degree in organic chemistry, medicinal chemistry, or a closely related discipline, and at least two years of practical experience synthesizing and characterizing drug molecules.

Pet. 33–34. Patent Owner agrees with this proposal, but adds that the ordinarily skilled person may also have "a bachelor's degree in chemistry, or a closely related discipline, and at least four years of practical experience synthesizing and characterizing drug molecules." Prelim. Resp. 14–15.

For this Decision, we adopt Petitioner's proposal. We do not, however, discern a substantive difference between the proposals that would affect our analysis. We also find that the relied-upon prior art demonstrates the level of skill in the art at the time of the invention. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required where the prior art reflects an appropriate level and a need for testimony is not shown).

C. Claim Construction

In an *inter partes* review, we interpret claim terms in an unexpired patent[12] based on the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming the broadest reasonable construction standard in *inter partes* review proceedings).[13] Under that standard, we presume a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257

---

[12] Patent Owner appears to have obtained a term extension for the '170 patent related to FDA approval for Jevtana® (cabazitaxel). *See* Patent Term Extension Certificate dated Feb. 4, 2014; *see also* Notice of Final Determination dated Oct. 20, 2013 (indicating expiration on Mar. 26, 2021).

[13] The Final Rule changing the claim construction standard in IPR proceedings does not apply here, as the Petition was filed before the rule's effective date, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,344 (Oct. 11, 2018). But, we do not perceive on this record that the construction of the challenged claims would be different depending on which standard is applied.

(Fed. Cir. 2007). We need only construe terms in controversy, and only to the extent necessary to resolve that controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

There is no claim construction dispute raised in this Petition. Petitioner states that the claims have their ordinary meaning and "do not require interpretation." Pet. 15. Patent Owner, for its part, states that "no term in claims 1 or 2 of the '170 patent requires construction." Prelim Resp. 15. So, for this Decision, we conclude that no express construction beyond the claim language itself is necessary.

D. History of the '170 Patent at the U.S. Patent Office and in Other Legal Proceedings

1. Prosecution History

On April 29, 1997, the Examiner rejected then-pending claim 17 (issued claim 1) as obvious over the taxanes in U.S. Patent No. 5,229,526 ("Holton '526") in combination with "Greene." Ex. 1004 (file history), 725–726; Ex. 1001, [56] (identifying, among the references cited, "Greene et al., "Protective Groups in Organic Synthesis," pp. 10–14, 2nd edition, 1991). According to the Examiner, although Holton '526 did "not specifically teach the instant R4 and R5 [i.e., C-10 and C-7] groups," the Examiner determined that Greene taught "the instant hydroxy protecting groups [methoxy groups] to be conventional." Ex. 1004, 727.

Applicants responded on October 29, 1997 with a declaration from one of the named inventors, Dr. Alain Commerçon. Ex. 1004, 665–666; *see also id.* at 680–689 (Oct. 23, 1997 Commerçon Decl.). Applicants argued

"that methoxy groups . . . at the 7- and 10-positions of the claimed compounds cannot be considered appropriate hydroxy protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups" described in Holton '526. *Id.* at 667. Applicants argued that Dr. Commerçon's testing showed "that when the 7,10-dimethoxy Test Compound is subjected to the mildly acidic conditions such as used in Holton . . . to deprotect taxane compounds . . . no removal of the methoxy groups of the Test Compound is observed." *Id.* at 670–671.

The Examiner responded on February 25, 1998, maintaining the rejection for obviousness, and adding U.S. Patent No. 5,489,601 ("Holton '601") to the combination of Holton '526 and Greene. *Id.* at 618–619. According to the Examiner, Holton '601 "teaches an analogous taxane wherein the C-7 and C-10 positions contain an alkoxy groups . . . [and] [i]t would have been prima facie obvious to replace the disclosed hydroxy protecting group of Holton ['526] with the hydroxy protecting groups as taught by Greene et al and Holton et al [i.e., Holton '601] to form the claimed compounds without the loss of the same utility." *Id.* at 619.

Applicants responded on April 23, 1998 with a second declaration from Dr. Commerçon. *Id.* at 589, 613–615. According to Applicants, Dr. Commerçon's second declaration provided testing data for compounds with and without methoxy groups at C-7 and C-10, and such testing allegedly showed "unexpectedly superior" properties with the compound of claim 17. *Id.* at 615; *see also id.* at 580–587 (April 23, 1998 Commerçon Decl.). In a Supplemental Response, Applicants also repeated their argument that methoxy groups could *not* serve as protecting groups at C-7 and C-10 of Holton's taxoids, and stated that the comparative testing was

offered merely "in support of an alternative argument." *Id.* at 326–327 (Apr. 27, 1998, Supplemental Response).

Then, following an interview with the Examiner, Applicants provided "Further Supplemental Remarks" on May 28, 1998. *Id.* at 298. Applicants stated that "[t]he purpose of the Supplemental Remarks" included "bring[ing] additional evidence to the Examiner's attention to further support Applicants' position that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups." *Id.* at 298–299. This additional evidence included citation and discussion related to two published European patent applications (EP 0 694 539 A1 ("EP '539") and EP 0 604 910 A1 ("EP '910")).[14] *Id.* at 299–302. Applicants asserted that "these two EP applications are quite similar to the disclosures of EP 639 577 (EP '577) and the Kant article in *Tetrahedron Letters* [(Ex. 1010, "Kant"),] which were cited in an Information Disclosure Statement on June 26, 1996." *Id.* at 299. Even if the references suggested methyl and methyl ether groups may be included at C-7 or C-10, Applicants nevertheless asserted that none of the references supported a finding that such groups, rather than being part of the final product, could or should function as removable hydroxy-protecting groups at those positions. *Id.* at 300–302. Applicants further explained that "the methyl groups at the 7- and 10-positions of the compound recited in claim 17 are not intended to be

[14] EP '539 is the European counterpart to the U.S. patent application that issued as Wong (Ex. 1011). Prelim. Resp. 8. The Supplemental Remarks mis-number EP '539 as EP 0 684 539, not EP 0 694 539. Ex. 1004, 299. A copy of EP '539, however, appears to have been submitted (Ex. 1004, 548) and the correct application number for EP '539 is identified in the IDS submitted by Applicants, which the Examiner initialed (*id.* at 293–295).

removed, i.e., converted to an H." *Id.* at 301. Hence, according to Applicants, the cited publications "further support Applicants' position that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups.[1]" *Id.* at 299–300, 302.[15]

On June 9, 1998, the Examiner entered a Notice of Allowability for claims 17 and 40 (issued claims 1 and 2), along with other pending claims. Ex. 1004, 292. The Examiner provided no further comment on the Applicants' arguments and gave no specific reasons for allowance. *Id.*

2. Prior Petition for Inter Partes *Review*

The Mylan Petition (*see supra*, Section II(A)) also challenged claims 1 and 2 of the '170 patent as being unpatentable for obviousness. Ex. 2011, 13–14. The two grounds advanced in the Mylan Petition are shown in the table below:

[15] In footnote 1 of the Supplemental Remarks, Applicants stated that neither the cited applications (EP '539 or EP '910), nor other art of record,

> remotely teaches or suggests the compound recited in present claim 17 which recites methoxy groups at **both** the 7- and 10-positions. In these references, the 7- and 10- positions do not overlap. Thus, there is no suggestion in these applications that the substituents at the 7- and 10- positions can be the same, let alone that they can **both** be methoxy.

Ex. 1004, 300 n.1.

Grounds	References	Basis	Claims
1	Kant and Klein[16]	§ 103	1 and 2
2	Colin,[17] Kant, and Klein	§ 103	1 and 2

Ex. 2011, 14.

For Ground 1, Mylan cited Kant's disclosure of paclitaxel and docetaxel analogues and, relying on Kant compound 20 and its favorable tubulin binding and cytotoxic properties, Mylan argued it would have been obvious to select that compound for modification. *Id.* at 2011, 5–6, 31.

Although Kant compound 20 differed from the compound of claim 1 of the '170 patent at only one position—including a hydroxyl group at C-7, rather than claim 1's methoxy group—Mylan argued that a methoxy substitution at C-7 was made obvious by Klein's teachings. Ex. 2011, 32. More specifically, Mylan asserted that Klein's analogous taxoid compounds having a methoxy group at C-7 significantly increased antitumor potency versus compounds with a hydroxyl group at that position (as in Kant's compound 20). *Id.* As for other substitutions described in Klein, particularly reduction of the carbonyl (CO) at C-9, Mylan argued the skilled artisan would not make such a change because it required a more complex process and additional synthetic steps, and Klein disclosed that it resulted in compounds with reduced potency against cancer cells. *Id.* at 34.

---

[16] L. L. Klein et al., *Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes*, in TAXANE ANTICANCER AGENTS (Chapter 20), 276–287 (Georg, G. et al. ed., American Chemical Society Symposium Series, 1994). Ex. 1016 or "Klein."

[17] Colin et al., US 4,814,470, issued Mar. 21, 1989 (hereafter "Colin").

Mylan also provided several rationales to support its combination of Kant and Klein. Among them, Mylan argued that it was "known in the art that the C-7 and C-10 hydroxyl groups of taxanes could be simultaneously modified," and that this "simultaneous" approach, wherein C-7 and C-10 would both be methylated, "would have been more straightforward than a chemoselective approach," as in Kant. *Id.* at 33–34 (citing evidence); *see also id.* at 21–25 (identifying rationales to modify C-7 and C-10 groups, including as "standard practice in drug design" to develop analogues with a range of lipophilicities; citing a known "general strategy" related to homologizing hydroxyl groups by substituting alkyl groups to increase lipophilicity; citing teachings by "Grover" and "Mellado" related to the C-7 and C-10 positions being available and "attractive" sites for small, non-bulky substitutions) (emphasis omitted). Mylan also emphasized that the skilled artisan would have been motivated to substitute methoxy groups at C-7 and C-10 in light of Kant's and Klein's teachings that compounds with a BOC-containing side chain and methoxy groups at C-7 (in Klein) and C-10 (in Kant) resulted in some of the most potent taxane analogues. *Id.* at 34.[18]

Mylan made similar arguments for Ground 2. Ex. 2011, 38–45. According to Mylan, Colin described docetaxel and taught that it had greater activity than paclitaxel against certain tumors, providing a reason to select docetaxel for improvement. *Id.* at 38–39. Again, citing teachings in Klein and Kant related to increased potency of taxanes with BOC-containing side chains and, respectively, C-7 and C-10 methoxy substitutions, Mylan argued that it would have been obvious to methylate both those positions to arrive at

[18] Mylan also offered testimony of Eric N. Jacobsen, Ph.D. in support of its challenge to claims 1 and 2 of the '170 patent. Ex. 2011, 3, *passim*.

cabazitaxel. *Id.* at 39–45 (discussing improved potency versus taxanes with a hydroxyl group at C-7 and an acetate group at C-10).

The Board found the Mylan Petition unpersuasive, and declined to institute trial. Ex. 2020. Among other things, the Board observed that Kant started with 10-DAB-III to synthesize paclitaxel analogues, and selectively substituted at only the C-10 position. *Id.* at 12. As Kant did not suggest further structural modifications to compound 20, the Board concluded that Kant cut against Mylan's challenge. *Id.*; *see also* Ex. 2021 (Rehearing Decision). The Board also concluded that Mylan's challenge was rooted in hindsight because, for example, nothing in Kant or Klein suggested that simultaneous substitution at the C-7 and C-10 positions would have been advantageous (e.g., such as to improve potency). *See, e.g.*, Ex. 2020, 12–13, 17. The Board was also unpersuaded the proposed changes—methylating both the C-7 and C-10 positions—would have been made in view of other known problems with taxanes, particularly poor aqueous solubility. *See id.* at 13–15. The Board made similar determinations as to the challenge based on Colin, Kant, and Klein. *Id.* at 17–20.

3. Court Proceedings

As described above, the validity of the '170 patent's claims has also been challenged in district court. *See supra* Section II(A) (*e.g.*, *Sanofi-Aventis US LLC et al. v. Fresenius Kabi USA, LLC*, No. 14-7869 (D.N.J. filed Dec. 17, 2014)). In a multi-defendant litigation, the district court conducted an eight-day bench trial and, on April 25, 2018, concluded that claims 1 and 2 of the '170 patent had not been shown to be invalid for obviousness. Ex. 1049 ("Decision") 83; *see also id.* at 16 (the defendants conceded that their accused products infringed claims 1 and 2 of the '170 patent).

As part of its Decision, the district court considered several prior art references, including references asserted in this Petition and the earlier Mylan Petition. Specifically, the district court considered and took testimony related to Commerçon, including Commerçon's disclosure on structure-activity relationships and about modifying portions of the taxane core. *See, e.g.*, Ex. 1049, 22; *see also* Ex. 2010 (Defendant's Post-Trial Brief), 14–15 (discussing Commerçon and its teaching about C-7 and C-10 being "flexible" positions on the taxane core for modification). The district court also received testimony about Kant, Wong, and Klein. Ex. 1049, 31–34.[19] Indeed, the Decision discusses Kant compound 20 and the methoxy modifications at the C-10 position of that compound (*id.* at 31–32), and also discusses Wong Example 2 and Klein as showing methoxy modifications at the C-7 position (*id.* at 31, 33); *see also* Ex. 2010, 15–18 (arguing that Wong, Klein, and other references would have motivated the skilled person to use a methoxy group at C-7, and that Kant and other references provided a motivation to use a methoxy group at C-10).

The district court also considered evidence about lead compounds. Ex. 1049, 29–30. According to the court, "[b]ased on the testimony and the prior art references, which reflect selection of both paclitaxel and docetaxel as a lead compound, the Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound." *Id.* at 30.

After considering the prior art and other evidence, however, the district court concluded that the assertions of obviousness were premised on impermissible hindsight. *Id.* at 36. For example, the court did not find

[19] The Decision at pages 17–21 provides an overview of the witnesses (fact and expert) whose testimony the court received. Ex. 1049, 17–21.

persuasive defendants' argument that a skilled person would have been motivated to make simultaneous methoxy substitutions at the C-7 and C-10 positions to form claim 1's compound. *Id.* at 37; *see also id.* at 36 ("[T]he Court finds that based on their selection of prior art references and the specific portions of those references upon which they relied, Dr. Kingston and Dr. Heathcock [defendants' experts] each 'cherry-picked' his way to cabazitaxel."). The court also further found that certain evidence on "secondary considerations" (e.g., alleged commercial success) weighed in plaintiffs'/Patent Owner's favor. *Id.* at 29, 41–43.

Defendants appealed the district court's Decision and, as pointed out by Patent Owner, the appeal is ready for oral argument before the Federal Circuit. Prelim. Resp. 28; *see Sanofi-Aventis U.S., LLC et al. v. Dr. Reddy's Laboratories, Inc. et al.*, No. 2018-1804 (Fed. Cir.); *see supra* n.3.

E. Discretionary Non-Institution

1. Legal Principles

Institution of *inter partes* review is discretionary. *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that "the PTO is permitted, but never compelled, to institute an IPR proceeding"). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that "[i]n determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." The Board also has discretion to institute proceedings pursuant to 35 U.S.C. § 314(a). *See, e.g., 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).

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors for consideration. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (informative) ("the *Becton Dickinson* factors"). Those factors are as follows:

1. the similarities and material differences between the asserted art and the prior art involved in examination;

2. the cumulative nature of the asserted art and the prior art evaluated during examination;

3. the extent to which the asserted art was evaluated during examination;

4. the extent of the overlap between the arguments made during examination and the manner in which a petitioner relies on the prior art or a patent owner distinguishes the prior art;

5. whether a petitioner has pointed out sufficiently how the Office erred in evaluating the asserted prior art; and

6. the extent to which additional evidence and facts presented in this petition warrant reconsideration of the prior art or arguments.

Office Patent Trial Practice Guide Update ("Trial Practice Guide Update"), referenced at 83 Fed. Reg. 39,989 (Aug. 13, 2018), at 12 (citing the *Becton Dickinson* factors). The *Becton Dickinson* factors are framed as comparing the art or arguments in a petition against what was before an examiner during prosecution. But, the Trial Practice Guide Update states as follows:

> Although the Board has considered the above-listed factors in the context of a trial petition that raises art that is the same or substantially the same as art presented previously during examination, parties to a IPR, PGR, or CBM proceeding may wish to analyze similar factors in the context of a trial petition involving art that is the same or substantially the same as art presented previously during . . . *an earlier-filed petition requesting an IPR*, PGR, or CBM review.

Id. at 13 (emphasis added).

The Board's discretion is also not necessarily limited based on the identity of the party that advanced the prior art or arguments in an earlier proceeding. To the contrary, the Board may, for example, deny a follow-on petition that advances substantially the same art or arguments even when filed by a different petitioner. *Unified Patents, Inc. v. PersonalWeb Techs., LLC*, Case IPR2014-00702, slip op. 7–9 (PTAB July 24, 2014) (Paper 13) (informative); *Google LLC v. Uniloc Luxembourg S.A.*, Case IPR2017-02067, slip op. 8–11 (PTAB Mar. 29, 2018) (Paper 10).

2. Summary of Arguments

Petitioner contends discretionary denial under § 325(d) is unjustified because "the references and arguments raised in this petition are substantially different [from the Mylan Petition] and have never been considered by the Board." Pet. 77–78. Petitioner points to its assertion of a different lead compound—paclitaxel, not Kant compound 20 or docetaxel. *Id.* at 78. And, Petitioner contends, the Commerçon and Wong references were not part of the obviousness challenge in the earlier Mylan Petition. *Id.* at 78;[20] *see also* Paper 13, 1–5.

[20] Petitioner also asserts that Bouchard was not part of the Mylan Petition. Pet. 78. As noted above, however, Petitioner relies on Bouchard for limited

Patent Owner counters, urging the Board to exercise its discretion and deny institution "because the arguments and prior art are cumulative to, and substantially the same as, those presented in the rejected Mylan IPR petition." Prelim. Resp. 20. On the lead compound, Patent Owner contends the distinction Petitioner draws is only "superficial" because "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." *Id.* at 20–21. Moreover, Patent Owner contends, Neptune "turns to Kant for the exact same reason Mylan did – to rationalize the substitution of the C-10 hydroxy of paclitaxel with a methoxy group on a compound with the docetaxel sidechain based on the allegedly improved activity of Kant Compound 20." *Id.* at 21; *see also id.* at 22 ("This is exactly the same rationale Mylan focused on for selecting Kant Compound 20 as its starting point for modification.").

Patent Owner further contends that Petitioner's allegation related to different prior art combinations is "similarly misleading." Prelim. Resp. 22. According to Patent Owner, "[b]oth Mylan and Neptune point to prior art compounds with a C-7 methoxy substitution to argue that replacing the C-7 hydroxyl with a methoxy group results in a taxane with improved activity." *Id.* at 22–23. Patent Owner contends that Petitioner "has simply swapped the teachings of Wong for the equivalent teachings in Klein." *Id.* at 23.

---

purposes related to certain elements of dependent claim 2 and, on that point, we are not persuaded that Bouchard adds substantively more than what the '170 patent itself admits are known and conventional formulating techniques, which disclosure was before the prior Board panel. *See supra* n.10; Ex. 2011, 36. Thus, we do not agree that Petitioner's reliance on Bouchard is sufficient to avoid discretionary denial under § 325(d).

Patent Owner contends that Commerçon "is cumulative of art and arguments that were before the Board" because the Mylan Petition likewise pointed to art disclosing the availability of specific positions, such as C-7 and C-10, on the taxane core for substitution, as well as the improved activity of analogues with a BOC-containing side chain. *Id.* at 23–25 (citing, e.g., Ex. 2011, 23, 26, 31, 40).

Patent Owner also contends Petitioner has simply recycled Mylan's failed arguments related to the motivation and likelihood of success in modifying the prior art to arrive at cabazitaxel. Prelim. Resp. 25–27. Patent Owner provides, for example, a side-by-side comparison of Mylan's and Petitioner's arguments about alleged improved activity of C-7 and C-10 methoxy analogues, and to a simplified synthesis wherein the exposed hydroxyl groups at C-7 and C-10 would be "simultaneously methylate[d]." *Id.* (comparing, for example, Pet. 46–47 with Ex. 2011, 45). The overlap in those arguments, Patent Owner argues, weighs in favor of the Board exercising its discretion under § 325(d). Prelim. Resp. 25–27.

In addition to the above, Patent Owner argues the Board should deny the Petition on a discretionary basis in view of the already completed district court proceedings and the pending appeal before the Federal Circuit where the same prior art as asserted here was, and remains, at issue. Prelim. Resp. 27–28 (citing, e.g., *Mylan Pharm. v. Bayer Intellectual Prop. GmbH*, Case IPR2018-01143 slip. op. at 13 (PTAB Dec. 3, 2018) (Paper 13) (denying petition under § 314(a) in light of, *inter alia*, the advanced stage of a pending district court litigation involving overlapping art, testimony, and claim construction)). According to Patent Owner, "the references used in the district court proceeding (*i.e.*, Commerçon, Kant, and Wong) are the

same as those now asserted by Neptune and used in the same way," and the "claim construction (plain meaning) is exactly the same." Prelim. Resp. 28.

3. Application of the Board's Discretion

After considering the parties' respective arguments, we are persuaded on this record that exercising our discretion under § 325(d) to deny institution is appropriate. *Becton Dickinson* factors (a)–(d) relate generally to whether and to what extent the same or substantially the same prior art and arguments from the Petition were considered previously by the Patent Office.[21] Patent Owner's arguments about the substantial similarities and overlap from the Mylan Petition and the present Petition, arguments with which we generally agree, are set forth at pages 18–27 of the Preliminary Response. We discuss further below.

We are unpersuaded that Petitioner's citation to paclitaxel as a lead compound is sufficient, on this record, to avoid discretionary denial of the Petition. Pet. 78; Paper 13, 2–3. 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

[21] The prosecution of the '170 patent before the Examiner is not decisive in whether we exercise our discretion under § 325(d) here; our focus is the earlier Mylan Petition. That said, we observe that the issue of C-7 and C-10 methoxy substitutions on analogous taxanes was squarely before the Examiner. *See supra* Section III(D)(1). With that issue before the Examiner, Applicants expressly called the Examiner's attention to, *inter alia*, Wong's European counterpart and Kant. Ex. 1004, 298–302. The Examiner did not comment on those references or Applicants' discussion of them, but instead allowed the claims. So, the extent of the Examiner's consideration of those references is inconclusive. These facts, however, present something more than arises when a petitioner relies on a reference buried in an IDS with no discussion of it whatsoever during prosecution.

Kant's analogues with a C-10 substitution. *Id.* The Board, 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 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.

Petitioner also contends that its challenge involves different art than the Mylan Petition: Commerçon, Kant, and Wong, rather than Kant and Klein. Pet. 77–78; Paper 13, 1, 3–4. But this contention elides the substantial similarities between the art and arguments presented in both this Petition and the Mylan Petition, as discussed below.

Petitioner states that it "provided a deep background on the state of the art and best practices in analog research," buttressed by Commerçon and its disclosure of modifiable portions of the taxane molecule. Paper 13, 1. Yet, Mylan likewise provided extensive evidence and discussion—at least eleven pages in its petition—on the background of taxanes and best practices

in analog research. Ex. 2011, 16–27. Mylan's discussion and evidence also addressed the same, or substantially the same, topics as those provided in Petitioner's "background" and Commerçon's disclosure. 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). Thus, as Patent Owner persuasively argues, Petitioner's background discussion and reliance on Commerçon is, on balance, cumulative to art and arguments that the Board already considered in the Mylan proceeding. Prelim. Resp. 23–24.

Neither are the alleged differences between Wong and Klein sufficient to avoid discretionary denial under § 325(d) on this record. To the contrary, we agree with Patent Owner that Petitioner has essentially swapped Wong's teachings for Klein for the same reason—to rationalize substitution of a methoxy group at C-7 with an expectation of producing more potent analogs. Prelim. Resp. 22–23.

Petitioner argues that Wong and Klein are not equivalent because Klein, unlike Wong, describes a removal of the C-9 carbonyl group and

includes a carboxyl group at C-10 for solubility and stability. Paper 13, 4. According to Petitioner, part of the Board's reasoning for denying the Mylan Petition related to whether the skilled artisan would have been motivated to make changes at C-9 and C-10 in view of Klein. *Id.* (citing Ex. 2020, 15–17). We do not agree that those alleged differences mean that discretionary denial is unjustified here. Wong's compounds include an acetate group (i.e., a carboxyl like Klein) at C-10, and Petitioner cites no suggestion in Wong that the C-10 position should be modified. *See, e.g.*, Ex. 1011, 12–13 (Examples 1–5 (each including "AcO" at C-10)). True, as Petitioner notes, Wong does not describe a potential reduction of the C-9 carbonyl like Klein. But Petitioner, like Mylan, raises substantially the same argument to explain why the skilled artisan would allegedly not make changes to the carbonyl at C-9—a position for modification known in the art. Indeed, Petitioner argues "Klein . . . showed that changing the double-bonded carbonyl group at C-9 to a hydroxyl group led to significant decreases in cytotoxicity" (Pet. 44 (citing Klein Table 1), and Mylan similarly argued "reduction at C-9 results in reduced potency" versus compounds that maintain the C-9 carbonyl (Ex. 2011, 34 (citing Klein Table 1)). We are not persuaded the differences between Wong and Klein outweigh their similarities, especially considering how Petitioner and Mylan used the respective references, along with the overlapping arguments related to Klein presented in both petitions.

Petitioner contends it relies on "[d]ifferent [a]rguments" to motivate simultaneous methylation at C-7 and C-10. Paper 13, 3 (emphasis omitted). Specifically, Petitioner contends, it supports its challenge with "best analog development practices" of (i) "homologation," the lengthening of accessible hydroxyl groups through addition of a carbon atom, and (ii) "increasing an

analog's stability through methylation to avoid a potential deleterious retro-aldol reaction." *Id.*

We are not persuaded Petitioner's arguments are materially different. To the extent there are differences, Petitioner does not adequately develop or support its arguments sufficiently to outweigh the substantial similarities between the Mylan Petition and this Petition as discussed above. First, the Mylan Petition and this Petition both unquestionably rely on the alleged simplicity of simultaneous methylation of exposed hydroxyl groups as motivating the proposed changes at C-7 and C-10. Prelim. Resp. 27; *compare* Pet. 46–47, *with* Ex. 2011, 1, 24–25, 33–34. Second, as to best analog development practices and homologation, this issue appears to have reasonably been raised in the Mylan Petition too. Ex. 2011, 22 (discussing, for example, "Burger" and "Grover," and homologizing hydroxyl groups by substituting small, non-bulky, alkyl groups). Third, on "potentially deleterious retro-aldol" chemistry, Petitioner devotes a mere two sentences of its nearly 80-page Petition to this point. Pet. 50. And the only support offered for Petitioner's contention is a single two-sentence paragraph in the Wood declaration, which is uncorroborated by any other cited evidence and similarly wanting for a detailed and thorough analysis. Ex. 1002 ¶ 249.[22] On this record, that is not enough to avoid exercise of the Board's discretion.

[22] In Petitioner's additional authorized briefing, Petitioner also mentions the Petition having addressed "solubility concerns . . . that would offset conflicting motivations by Klein." Paper 13, 4. But here again, this appears to be an argument that parallels arguments that were raised, but rejected, in the Mylan Petition. *Compare* Pet. 49–50, 58, *with* Ex. 2011, 25–26, 35, 47 (relating to known techniques of formulating lipophilic taxanes with solubility-enhancing adjuvants or diluents (e.g., Cremophor EL)).

Turning to *Becton Dickinson* factors (e) and (f), those factors look to whether the Petitioner has made an adequate case for reconsidering the prior art or arguments. Petitioner has not made an adequate showing here. Petitioner does not, for example, persuasively identify any error in the prior Board panel's consideration of the prior art or arguments. Instead, Petitioner's argument on discretionary denial under § 325(d) is premised on its challenge being substantially different than in the Mylan Petition. For the reasons explained above, that argument is unavailing.

Finally, although the stage of related litigation has been, more often, a factor considered when weighing the exercise discretion under § 314(a),[23] the completed district court proceeding and pending Federal Circuit appeal related to the validity of the '170 patent are worthy of consideration here—even if only as an adjunct to our analysis of the *Becton Dickinson* factors and § 325(d) discretion provided above. At minimum, as explained elsewhere by the Board, "the overall goal of the AIA [is] to 'make the patent system more efficient by the use of post-grant review procedures.'" *Mylan*, Case IPR2018-01143, slip op. at 14 (Paper 13) (quoting *General Plastic*, Case IPR2016-01357, slip op. at 16–17 (Paper 19)). We do not see how that goal is served by ignoring or declaring irrelevant the related and ongoing litigation history of the '170 patent based on the facts presented in this record, even if our analysis here focuses on § 325(d) discretion. We discuss further below.

---

[23] *See, e.g.*, *Mylan*, Case IPR2018-01143, slip op. at 13–14 (Paper 13) (citing *NHK Spring Co. v. Intri-Plex Techs., Inc.*, Case IPR2018-00752, slip op. at 19–20 (PTAB Sept. 12, 2018) (finding the advanced stage of a pending district court case addressing the same art is an additional factor for consideration under § 314(a)).

Petitioner argues the district court's decision "has no bearing on this petition." Pet. 34–35 ("[A]though the District Court considered approximately fifteen publications, including several of the ones asserted in this petition, it merely listed the references in a disparate fashion and did not consider the express combinations or bases asserted in this petition."); *see also* Paper 13, 4–5. We disagree. The district court's decision is relevant to Petitioner's challenge based on Commerçon, Kant, and Wong. Indeed, as explained above, the exact same prior art was discussed in detail by the court in reaching its decision on the issue of the obviousness of the same claims of the same patent. *See supra* Section III(D)(3).

Given the district court's analysis and the briefing on appeal, it is also reasonable to conclude that any forthcoming decision from the Federal Circuit (the Board's reviewing court) would address directly the alleged obviousness of claims 1 and 2 in light of Commerçon, Kant, and Wong, among other references.[24] And there appears to be no difference in claim construction that might make the court proceedings less relevant to Petitioner's challenge. Prelim. Resp. 28; Ex. 1049, *passim*. Moreover, as detailed above, the Board already declined institution of a substantially

[24] For example, defendants' briefing on appeal argues, *inter alia*, that the district court erred in finding no motivation to modify C-7 and C-10 when the teachings of Commerçon, Kant, and Wong (along with other references) are considered. *See, e.g.*, *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*, No. 2018-1804, Document 68, 22–24 (Fed. Cir. filed Aug. 20, 2018) (arguing, *inter alia*, that the court's "analysis failed to apply the teachings of *Commerçon* . . . that the C-7 and C-10 positions were 'flexible' and could thus be readily modified without losing biological activity" and "[b]ased on these errors, the court erroneously characterized the [expert] testimony . . . regarding the C-7 and C-10 position data from *Kant*, *Klein*, and *Wong* references as 'cherry pick[ing].'").

similar obviousness challenge to the same claims of the same patent. In short, the stage and significant subject-matter overlap of the court proceedings, with a decision from the Federal Circuit likely to come before the Board would complete the trial proceedings requested here by Petitioner (assuming the Board were to institute review), further tilt in favor of restraint and discretionary denial of this Petition.

IV. CONCLUSION

For the foregoing reasons, we exercise our discretion under 35 U.S.C. § 325(d) not to institute review in this proceeding on claims 1 and 2 of the '170 patent.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and we do not institute *inter partes* review of any claim of the '170 patent based on the grounds asserted in this Petition.

PETITIONER:

Alexander E. Gasser
Sarah Spires
SKIERMONT DERBY LLP
agasser@skiermontderby.com
sspires@skiermontderby.com

PATENT OWNER:

Daniel J. Minion
Dominick A. Conde
William E. Solander
Melinda R. Roberts
VENABLE LLP
DMinion@Venable.com
DConde@Venable.com
WSolander@Venable.com
MRRoberts@Venable.com