

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AGILA SPECIALTIES INC. and MYLAN LABORATORIES LIMITED,
Petitioner,

v.

CEPHALON, INC.,
Patent Owner.

Case IPR2016-00026
Patent 8,791,270 B2

Before JACQUELINE WRIGHT BONILLA, ZHENYU YANG, and
TINA E. HULSE, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Agila Specialties Inc. and Mylan Laboratories Limited (collectively, “Petitioner”) filed a Petition for an *inter partes* review of claims 1–23 of U.S. Patent No. 8,791,270 B2 (“the ’270 patent,” Ex. 1001). Paper 3 (“Pet.”). Cephalon, Inc. (“Patent Owner”) timely filed a Preliminary Response. Paper 12 (“Prelim. Resp.”). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Therefore, we deny the Petition for an *inter partes* review. See 35 U.S.C. § 314(a).

Related Proceedings

According to the parties, Patent Owner previously asserted the ’270 patent against Petitioner in *Cephalon, Inc. v. Agila Specialties Inc.*, Case No. 1:14-cv-01237 (D. Del.). Pet. 10; Paper 6. This case later was consolidated with several other cases filed by Patent Owner, asserting the ’270 patent against several other entities. Pet. 9–10; Paper 6.

Petitioner previously filed a Petition for an *inter partes* review of U.S. Patent No. 8,436,190 B2, a patent in the same family as the ’270 patent. *Agila Specialties Inc. v. Cephalon, Inc.*, IPR2015-00503, Paper 4. We instituted trial to review the patentability of certain claims, but denied review of others. *Id.*, Paper 10 (PTAB July 20, 2015). The parties subsequently settled, and we terminated the case. *Id.*, Paper 21 (PTAB Nov. 16, 2015).

The '270 Patent

The '270 patent is directed to stable pharmaceutical compositions of nitrogen mustards, in particular, lyophilized bendamustine, which can be used to treat various disease states, especially neoplastic diseases and autoimmune diseases. Ex. 1001, 3:20–24.

Bendamustine was first synthesized in East Germany in 1963. *Id.* at 2:1–2. At the time of the '270 patent invention, bendamustine was marketed in Germany under the name Ribomustin® to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer. *Id.* at 2:5–9.

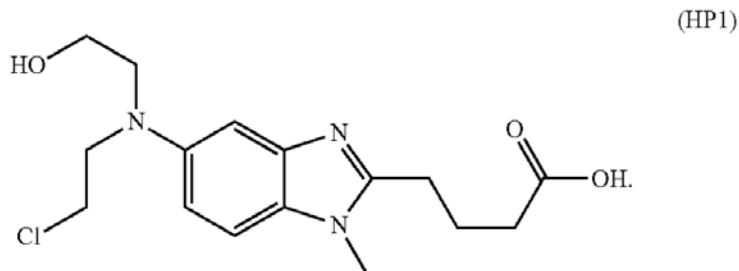
According to the '270 patent, “[b]endamustine degrades rapidly in water alone and forms predominantly the hydrolysis product, HP1 (monohydroxy bendamustine).” *Id.* at 21:3–5. Other degradants include the dimer of bendamustine (BM1 dimer), bendamustine ethylester (BM1EE), and BM1DCE. *Id.* at 21:30–50.

The '270 patent discloses stable pharmaceutical compositions prepared from bendamustine, in particular, “formulations for the lyophilization of bendamustine HCl.” *Id.* at 12:27–30. According to the '270 patent, the lyophilized powder obtained from such formulations is more easily reconstituted and has a better impurity profile than Ribomustin®. *Id.* at 12:30–37.

Illustrative Claims

Among the challenged claims, claims 1 and 7 are independent. They read as follows:

1. A pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9% (area percent of bendamustine) of HP1:



7. A pharmaceutical composition of bendamustine hydrochloride, containing less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants.

Dependent claims 2–6 and 8–19 also are directed to pharmaceutical compositions. Claims 2–6 depend, directly or indirectly, from claim 1, while claims 8–19 depend, directly or indirectly, from claim 7.

Claim 20 is a method claim that depends from claim 7. It reads:

20. A method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to claim 7.

Each of claims 21 –23 is a method claim that depends directly from claim 20.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims	Basis	Reference(s)
1, 2, 7–10, 13–16, 19, and 20	§ 102(b)	Maas ¹

¹ Maas et al., *Stability of Bendamustine Hydrochloride in Infusion Solutions*, 49 PHARMAZIE 775–77 (1994) (Ex. 1007, “Maas”).

Claims	Basis	Reference(s)
1–20	§ 103	Maas and Teagarden ²
13 and 19	§ 103	Maas, Teagarden, and Gust ³
20–23	§ 102	Maas, Teagarden, and The Rote Liste ⁴

In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Samuel H. Yalkowsky. Ex. 1002.

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1278–81 (Fed. Cir. 2015), *cert. granted sub nom. Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under that standard, absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

² Teagarden and Baker, *Practical Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems*, 15 EUR. J. PHARM. SCI. 115–33 (2002) (Ex. 1006, “Teagarden”).

³ Gust and Krauser, *Investigations on the Stability of Bendamustin, a Cytostatic Agent of the Nitrogen Mustard Type, I. Synthesis, Isolation, and Characterization of Reference Substances*, 128 CHEMICAL MONTHLY 291–99 (1997) (Ex. 1008, “Gust”).

⁴ The Rote Liste 2003 (Ex. 1005, “the Rote Liste”).

Petitioner proposes to construe the terms “lyophilized preparation” and “lyophilized composition,” “pharmaceutical composition,” “area percent of bendamustine,” “bendamustine degradants,” “time zero after reconstitution,” and “about.” Pet. 13–16. Patent Owner states that for the purpose of this Decision, it accepts Petitioner’s proposed constructions. Prelim. Resp. 16. We similarly accept Petitioner’s proposed constructions for purposes of this Decision. Specifically, we accept that “in the context of the claims and specification of the ’270 patent, one of ordinary skill in the art would construe the claim term ‘about 0.9% (area percent of bendamustine)’ to include ‘0.96% (area percent of bendamustine).’” Pet. 16.

Prior Art Disclosures

Maas discloses bendamustine as “very unstable in an aqueous solution.” Ex. 1007, 4. It explains that “[d]ue to the rapidly progressing hydrolysis of aqueous bendamustine hydrochloride solutions, only freshly made up solutions . . . must be injected immediately after their preparation.” *Id.* at 5. In a stability test, Maas identified bendamustine hydrochloride by reverse-phase HPLC. *Id.*

Teagarden teaches that using non-aqueous co-solvent systems in freeze-drying pharmaceutical products has numerous advantages, including “increased pre-dried bulk solution or dried product stability.” Ex. 1006, 115. Specifically, according to Teagarden, the *tert*-butanol (“TBA”)/water combination “possesses a high vapor pressure, freezes completely in most commercial freeze-dryers, readily sublimates during primary drying, can increase sublimation rates, and has low toxicity.” *Id.* In contrast, other co-solvent systems do not freeze completely in commercial freeze-dryers, are

more difficult to use, and often result in unacceptable freeze-dried cakes. *Id.* In addition, Teagarden teaches that the TBA/water co-solvent system “significantly reduced” the degradation rate of certain water unstable drugs. *Id.* at 117–18.

Gust teaches the synthesis, isolation, and characterization of bendamustine and its derivatives. Ex. 1008, 291–99. According to Gust, bendamustine is synthesized by cleaving dichloroester⁵ with HCl, whereas dichloroester can be formed by esterification of bendamustine in ethanolic HCl. *Id.* at 292–93. Gust also teaches that dichloroester is present in crude bendamustine samples. *Id.* at 298.

The Rote Liste teaches Ribomustin® is a dry substance and specifies that “1 injection vial with 55 mg . . . dry substance” contains “bendamustine HCl 25 mg.” Ex. 1005, 3. It also lists “M. Hodgkin (Stages II – IV), Non-Hodgkin lymphoma, Plasmacytoma, Chron. lymphat. leukemia, mammary carcinoma” under “Treatment Indications.” *Id.*

Anticipation Ground

Petitioner argues that Maas anticipates claims 1, 2, 7–10, 13–16, 19, and 20. Pet. 22–33. Based on the current record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

⁵ According to Dr. Yalkowsky, dichloroester in Gust is the same as bendamustine ethylester in the ’270 patent. Ex. 1002 ¶ 87.

Claims 1, 2, 10, and 16

Each of claims 1, 2, 10, and 16 requires the bendamustine composition to contain “not more than about 0.9% (area percent of bendamustine) of HP1.” According to Petitioner, Maas shows an HPLC chromatogram of reconstituted Ribomustin® with a “characteristic peak of bendamustine” and a peak for a decomposition product, “presumably the monohydrolysis product,” i.e., HP1. Pet. 23 (citing Ex. 1007, 5). Petitioner contends that “[t]he peak corresponding to HP1 is small relative to the peak corresponding to bendamustine in the figure of Maas.” *Id.*

Petitioner acknowledges “[t]hough Maas shows a small amount of HP1 present, Maas does not state a precise percent (area percent of bendamustine) amount of the degradants present in Ribomustin®.” *Id.* at 21. Nevertheless, Petitioner argues that the ’270 patent provides the requisite data. *Id.* Specifically, Petitioner refers to Table 13 of the ’270 patent and points out that one batch of Ribomustin®, 02K27, contains 0.93% area of HP1. *Id.* at 23. This, according to Petitioner, is equal to 0.96% (area percent of bendamustine), and, under Petitioner’s proposed construction, satisfies “about 0.9% (area percent of bendamustine),” as required by claim 1. *Id.* at 24.

In sum, Petitioner contends, because “Maas shows a small amount of HP1 degradant, relative to bendamustine, present in reconstituted Ribomustin®,” and because “[t]he ’270 patent quantifies HP1 present in reconstituted Ribomustin®, including lot 02K27, which had an amount of HP1 that falls within the scope of claim 1,” Maas anticipates claim 1. *Id.* at 25. We are not persuaded.

To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). Petitioner bases its anticipation argument on an inherency theory. Pet. 24–25. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). “Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

Here, Table 13 of the '270 patent reports the impurity profile of four batches of Ribomustin®. Ex. 1001, 30:33–45. As Patent Owner correctly points out, Petitioner relies on the data from only a single batch with the lowest HP1 content. *See* Prelim. Resp. 21. Petitioner fails to mention that for each of the other three batches of Ribomustin® tested, the HP1 content is over 1% (area percent of bendamustine), outside of the required range of “not more than about 0.9% (area percent of bendamustine).” In other words, Table 13 shows that the amount of HP1 in reconstituted Ribomustin® is not *necessarily* “not more than about 0.9% (area percent of bendamustine),” as required by claims 1, 2, 10, and 16.⁶ As a result, based on the current record, we are not persuaded that Maas inherently anticipates those claims.

⁶ Moreover, even if the other three batches of Ribomustin® tested in Table 13 contained the claimed range of HP1, Petitioner’s argument still would fail because Petitioner presents an insufficient connection between the Ribomustin® samples disclosed in Table 13 of the '270 patent with the

Claims 7–10, 13–16, 19, and 20

Claim 7 requires the composition of bendamustine hydrochloride to contain “less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants.” Petitioner concedes that Maas itself “does not state a precise percent (area percent of bendamustine) amount of the degradants present in Ribomustin®.” Pet. 21. Instead, Petitioner again refers to the test data in Table 13 of the ’270 patent to support its argument that Maas inherently anticipates the challenged claim 7. *Id.* at 26.

According to Petitioner, Ribomustin® compositions tested in the ’270 patent “contained from 1.68% to 2.56% (area percent of bendamustine) of bendamustine hydrochloride degradants.” *Id.* (citing Ex. 1001, 30:35–45). Thus, Petitioner concludes, “the composition disclosed by Maas contained amounts of bendamustine hydrochloride degradants falling well within the ‘less than or equal to 4.0% (area percent of bendamustine)’ recited in claim 7.” *Id.* at 26–27.

Patent Owner counters that Table 13 of the ’270 Patent does not shed light on the contents of the reconstituted pharmaceutical composition described in Maas because “[u]nlike Maas, Table 13 does not report the content of a reconstituted pharmaceutical composition.” Prelim. Resp. 24. We agree.

Ribomustin® samples analyzed in Maas. That is, Petitioner has not established that the Ribomustin® analyzed in Maas necessarily has the claimed amount of HP1.

As Petitioner recognizes, Maas discloses “a pharmaceutical composition (Ribomustin®) reconstituted from a lyophilized preparation of bendamustine hydrochloride.” Pet. 26 (citing Ex. 1007, 4–5). In Maas, bendamustine hydrochloride “was dissolved first in 10 mL of water and then diluted with 0.9% sodium chloride solution to 100 mL.” Ex. 1007, 5. In contrast, samples of Ribomustin® tested in Table 13 of the ’270 patent were dissolved with 200 mL of methanol. Ex. 1001, 29:29–31, 30:33–34. Maas acknowledges that bendamustine “is very unstable in an aqueous solution.” Ex. 1007, 4. And the ’270 patent confirms this: “Bendamustine degrades quickly in water but the stability of bendamustine increase with increasing alcohol concentrations.” Ex. 1001, 31:55–57.

Thus, we agree with Patent Owner that “[i]f the Ribomustin analyzed in the ’270 Patent had (as in Maas) been dissolved in water and diluted in a solution of sodium chloride and water, instead of being dissolved in pure methanol, the bendamustine would have degraded further.” Prelim. Resp. 20. In other words, the fact that Table 13 of the ’270 patent reports Ribomustin® compositions containing “from 1.68% to 2.56% (area percent of bendamustine) of bendamustine hydrochloride degradants” does not mean reconstituted Ribomustin® in Maas *necessarily* would also contain “less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants,” as claim 7 requires. As a result, based on the current record, we are not persuaded that Maas inherently anticipates claim 7 or its dependent claims, claims 8–10, 13–16, 19 and 20.

Obviousness Grounds

Petitioner asserts that claims 1–20 would have been obvious over Maas and Teagarden, claims 13 and 19 would have been obvious over Maas Teagarden, and Gust, and claims 20–23 would have been obvious over Maas Teagarden, and the Rote Liste. Pet. 33–57. Based on the current record, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in these assertions.

Petitioner refers to Maas for teaching that “bendamustine hydrochloride is highly unstable in water, resulting in the presence of the HP1 degradant in the reconstituted Ribomustin® composition.” *Id.* at 35. As a result, Petitioner argues, an ordinary artisan would have had a reason to “minimize the amount of HP1 and other degradants in a pharmaceutical composition of bendamustine hydrochloride.” *Id.*

Petitioner next refers to Teagarden for teaching using TBA to improve the stability of unstable drugs in solution. *Id.* at 36 (citing Ex. 1006, 117, 118). Specifically, Petitioner points to Teagarden for describing using TBA/water in five drug formulations. *Id.* According to Petitioner, Teagarden teaches that the TBA/water co-solvent system improves the stability of those water unstable drugs. *Id.* (citing Ex. 1006, 117 (reporting that for one drug, the first-order degradation rate constant “was significantly reduced compared to water”), 118 (reporting that using TBA slowed solution state degradation of another drug “by a factor of approximately 4–5”)). Also according to Petitioner, Teagarden predicts that this stabilizing effect “would be expected to be observed for many other drug products which are degraded in the presence of water.” *Id.* (citing Ex. 1006, 118). Thus,

Petitioner argues, one of ordinary skill in the art would have lyophilized bendamustine hydrochloride from a TBA/water solution with a reasonable expectation of success “in reducing the small amount of HP1 present in Ribomustin® up to four- to five-fold, which would fall well below 0.9% (area percent of bendamustine), as recited in claim 1” (*id.*), and “in arriving at a composition containing substantially less than the amount of bendamustine degradants in Ribomustin®,” as recited in claim 7 (*id.* at 41). We are not persuaded.

For purposes of this Decision, we assume, without deciding, that (1) one of ordinary skill in the art would have had a reason to combine the teachings of Maas, Teagarden, and other asserted prior art references; and (2) lyophilizing Ribomustin® from a TBA/water solution would reduce the degradation rate by “a factor of approximately 4–5.” We nevertheless are not persuaded that the prior art would have rendered the challenged claims obvious.

As Petitioner acknowledges, “Maas does not state a precise percent (area percent of bendamustine) amount of the degradants present in Ribomustin®” (Pet. 21), and “Teagarden does not teach a composition of bendamustine hydrochloride” (*id.* at 22). Rather, Petitioner characterizes that the HPLC chromatogram shows “a small amount of HP1” in reconstituted Ribomustin®. *Id.* Reducing an unspecified “small amount of HP1” by “a factor of approximately 4–5,” however, does not translate into “not more than about 0.9% (area percent of bendamustine) of HP1,” as recited in claim 1, or “less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants,” as recited in claim 7. Thus, we

agree with Patent Owner that “Maas and Teagarden taken together still would not suggest specific limits on the amounts of the degradants in reconstituted Ribomustin formulations,” as recited in claims 1 and 7. *See* Prelim. Resp. 34. Petitioner also does not otherwise argue that the general knowledge of a skilled artisan would have suggested the specific amounts of the degradants in reconstituted Ribomustin® recited in claims 1 and 7.

For claims 13 and 19, Petitioner relies on Gust solely for the teaching that bendamustine ethylester is present as an impurity in crude bendamustine and that it is formed when bendamustine reacts with ethanol. Pet. 53 (citing Ex. 1008, 292, 293, 298, 299). For claims 20–23, Petitioner relies on the Rote Liste solely for teaching the treatment indications for Ribomustin®. *Id.* at 55–56. In other words, neither Gust nor the Rote Liste remedies the deficiencies of Mass and Teagarden, as discussed above.

Thus, based on the current record, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the challenged claims would have been obvious over Mass, Teagarden, Gust, and the Rote Liste. *See In re Kao*, 639 F.3d 1057, 1066 (Fed. Cir. 2011) (“[I]t matters greatly whether anything the skilled artisan would be prompted by the prior art to do is *in fact* within the scope of the . . . claim.”).

Real Party-in-Interest

Patent Owner urges that we deny the Petition because Petitioner fails to identify Mylan Inc. and Mylan Pharmaceuticals Inc. as real parties-in-interest with respect to the Petition. Prelim. Resp. 10–15. Because Petitioner has not established a reasonable likelihood that it would prevail in

showing the unpatentability of at least one challenged claim, we need not reach the real party-in-interest issue.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of any of the challenged claims.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 1–23 of the '270 patent is *denied*.

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