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 IPR2015-00503
Patent 8,436,190 B2

Before LINDA M. GAUDETTE, JACQUELINE WRIGHT BONILLA, and ZHENYU YANG, Administrative Patent Judges.

YANG, Administrative Patent Judge.

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


For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1, 4, and 7, we institute an *inter partes* review of these claims. Petitioner, however, has not established a reasonable likelihood that it would prevail in showing the unpatentability of claims 2, 3, 5, 6, 8, and 9. Therefore, we deny the Petition regarding the challenges to those claims.

*Related Proceedings*


*The ’190 Patent*

The ’190 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, 2:66–3:3. According to the ’190 patent, “the term ‘lyophilized powder’ or ‘lyophilized preparation’ refers to any solid material obtained by lyophilization, i.e., freeze-drying of an aqueous solution.” Id. at 9:1–3.

Bendamustine was first synthesized in East Germany in 1963. Id. at 1:50–51. At the time of the ’190 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 1:53–57.

The ’190 patent discloses stable pharmaceutical compositions prepared from bendamustine, in particular, “formulations for the lyophilization of bendamustine HCl.” Id. at 12:7–10. According to the ’190 patent, the lyophilized powder obtained from such formulations is more easily reconstituted and has a better impurity profile than Ribomustin®. Id. at 12:10–16.

Illustrative Claim

Among the challenged claims, claim 1 is the sole independent claim. It reads:

1. A pharmaceutical composition comprising bendamustine or bendamustine hydrochloride, mannitol, tertiary-butyl alcohol and water.
Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

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In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Raj Suryanarayanan. Ex. 1002.

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\(^1\) The Rote Liste 1996 (Ex. 1006, “the Rote Liste”).
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). Under that standard, and 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).

Petitioner requests that we construe the term “made from.” Pet. 18–19. The term “made from” appears in claim 4, which reads, “[a] lyophilized pharmaceutical composition made from the pharmaceutical composition according to claim 1.” Petitioner argues that claim 4 and claims dependent therefrom are directed to lyophilized products, made from the process of lyophilizing the pharmaceutical composition of claim 1. *Id.* at 18. Thus, Petitioner asserts the term means “made from the process of lyophilizing.” *Id.* Patent Owner disagrees. Prelim. Resp. 19. According to Patent Owner, the plain language of the claim indicates that “made from” refers to the composition of claim 1, and not the process of lyophilizing. *Id.* We agree with Petitioner that claim 4 and claims dependent therefrom are product-by-process claims.

A product-by-process claim is “one in which the product is defined at least in part in terms of the method or process by which it is made.” *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 158 n. (1989). Claim
4 recites a pharmaceutical composition made from the composition of claim 1. It specifies that the pharmaceutical composition is “lyophilized.” In other words, the pharmaceutical composition of claim 4 is defined in part by the lyophilization process. Thus, we adopt Petitioner’s proposed construction and interpret the term “made from” to mean “made from the process of lyophilizing.”

Petitioner also proposes to construe the terms “lyophilized,” “said pharmaceutical composition,” “containing not more than about 0.5%,” and “about.” Pet. 17–21. Patent Owner states that these terms “need no construction to determine whether to institute the proceeding.” Prelim. Resp. 19. We agree with Patent Owner, and thus, decline to construe these terms expressly for purposes of this Decision.

*Patentability Analysis*

**Prior Art Disclosures**

The Rote Liste discloses a dry substance and specifies that “1 vial with 55 mg of dry substance contains: bendamustine HCl 25 mg. Other components: mannitol.” Ex. 1006, 8.

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. 1007, 115. Specifically, according to Teagarden, the *tert*-butanol [TBA]/water combination “possesses a high vapor pressure, freezes completely in most commercial freeze-dryers, readily sublimes 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. Ex. 1007, 117–18.

Nuijen teaches formulating 500 mg/mL solution of aplidine in 40% (v/v) TBA containing 25 mg/mL D-mannitol. Ex. 1008, 193. Aplidine is an antitumor agent. Id. Nuijen’s data show that aplidine lyophilized from this formulation is stable for at least 1 year when stored at 2–8°C in the dark. Id.

Gust teaches the synthesis, isolation, and characterization of bendamustine and its derivatives. Ex. 1009, 291–99. According to Gust, bendamustine is synthesized by cleaving dichloroester 5 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.

35 U.S.C. § 325(d)

Patent Owner asks us to deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 21–24. According to Patent Owner, during prosecution of the ’190 patent, the examiner allowed the challenged claims despite having knowledge of prior art with essentially the same teachings as those in the references asserted here. Id. at 21–23.

5 According to Dr. Suryanarayanan, dichloroester in Gust is the same as bendamustine ethylester in the ’190 patent. Ex. 1002 ¶ 54.
The statute allows, but does not require, the Director to deny a petition if “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). Here, even if we were to agree with Patent Owner that the prior art before the examiner and those asserted in the Petition might be considered “substantially the same prior art” under § 325(d), we decline to exercise our discretion to deny the Petition on this basis in this case.

**Obviousness over the Rote Liste and Teagarden**

Petitioner asserts that claims 1–9 would have been obvious over the Rote Liste and Teagarden. Pet. 21–34. Based on the current record, we determine that Petitioner has shown a reasonable likelihood that it would prevail in this assertion with regard to claims 1, 4, and 7, but not claims 2, 3, 5, 6, 8, and 9.

**Claim 1**

Citing the Declaration of Dr. Suryanarayanan, Petitioner argues that one of ordinary skill in the art would have understood bendamustine HCl in the Rote Liste as resulting from the lyophilization of a liquid solution. Pet. 22 (citing Ex. 1002 ¶ 69). Petitioner refers to the prosecution history of the ’190 patent, in which the applicants stated that “[p]rior to the [’190 patent] invention, bendamustine was historically lyophilized from a solution of ethanol, water, mannitol, and bendamustine.” Id. (citing Ex. 1005, 367). At the time of the ’190 patent invention, Petitioner asserts, it was known that bendamustine, a nitrogen mustard compound, is highly reactive and unstable
in aqueous solutions. *Id.* (citing Ex. 1009, 292; Ex. 1010,6 4). Petitioner contends that Teagarden teaches using TBA to improve the stability of unstable drugs in solution. *Id.* at 23 (citing Ex. 1007, 117). Thus, according to Petitioner, a skilled artisan, concerned with the instability of bendamustine, would have looked to Teagarden to address the problem. *Id.* at 24.

Petitioner also points to Teagarden for describing using TBA/water in five drug formulations. *Id.* (citing Ex. 1007, 117–18). According to Petitioner, the TBA/water co-solvent system improves the stability of those water unstable drugs. *Id.* at 25 (citing Ex. 1007, 117 (reporting that the first-order degradation rate of alprostadil in 20% v/v TBA/water “was significantly reduced”), 118 (reporting that using TBA slowed solution state degradation of treceitilde fumarate “by a factor of approximately 4–5”)). Thus, Petitioner argues, one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the composition of claim 1 based on the combined teachings of the Rote Liste and Teagarden. *Id.* at 24.

Patent Owner contends that Petitioner combines the Rote Liste and Teagarden through hindsight reasoning. Prelim. Resp. 24. According to Patent Owner, even though bendamustine compositions, such as Ribomustin®, had been marketed in Germany for more than forty years, only the inventors of the ’190 patent set out to create a lyophilized formulation that is easier to reconstitute and has a better impurity profile. *Id.*

at 24. Patent Owner asserts that none of the references cited in the Petition “identified any problem with [the then] existing bendamustine/mannitol compositions.” Id. at 25. And even if any problems associated with bendamustine had been identified, Patent Owner further argues, the possible approaches to solving those problems “were not known or finite,” Petitioner does not present any evidence to show that TBA would have solved those problems, and the TBA solution was not predictable. Id. at 26–29. We disagree.

Patent Owner’s arguments are based on the premise that at the time of the invention, only the inventors of the ’190 patent identified a need for lyophilized formulations of bendamustine that would be “easier to reconstitute” and would have “a better impurity profile” than the then-available lyophilized powder of bendamustine. Id. at 10, 24 (both citing Ex. 1001, 2:29–32). The law, however, “does not require that the references be combined for the reasons contemplated by the inventor.” In re Beattie, 974 F.2d 1309, 1312 (Fed. Cir. 1992). Indeed,

[T]he problem motivating the patentee may be only one of many addressed by the patent’s subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.


Such is the case here. Petitioner contends that a skilled artisan “would have been aware as a matter of basic knowledge that bendamustine is a
nitrogen mustard compound and thus highly reactive and unstable in aqueous solutions.” Pet. 22. Petitioner’s argument is supported by evidence before us at this time. For example, Maas teaches that bendamustine “is very unstable in an aqueous solution.” Ex. 1010, 4. It explained 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. Maas determined the stability ($t_{90}$) of Ribomustin® in aqueous NaCl solution (0.25 mg/ml, 0.9% NaCl solution) is 120 hours at 4°C and 9 hours at 23°C. Id. at 5. In another example, Gust recognized that “bendamustin[e] hydrolyzes in water similar to other N-lost compounds.” Ex. 1009, 292. Gust also cited the stability data reported in Maas. Id. Thus, we are persuaded that, at the time of the ’190 patent invention, one of ordinary skill in the art would have been motivated to improve the stability of Ribomustin®, the bendamustine drug on the market.

As Petitioner points out, Teagarden identifies using TBA in pre-lyophilization formulation for unstable drugs. Pet. 5–6 (citing Ex. 1002 ¶¶ 45–46), id. at 25 (citing Ex. 1007, 117, 118). Teagarden explains:

A major challenge in developing a sterile injectable product can be its instability in solution. Most freeze-dried products are developed as this dosage form in order to circumvent poor stability. The manufacture of a freeze-dried product necessitates that the product is usually first manufactured as a solution, filtered to sterilize, aseptically filled, and finally lyophilized to remove the solvents.
Ex. 1007, 117. According to Teagarden, the organic solvents used in the pre-lyophilization solution “can have a profound effect on the chemical stability.” Pet. 25 (citing Ex. 1007, 117).

Specifically, Teagarden describes that freeze-drying unstable drugs from a TBA/water solution “significantly reduced” the degradation rate, sometimes “by a factor of approximately 4–5.” Id. (citing Ex. 1007, 117, 118). Teagarden comments that the decreased degradation rate enables manufacturing at ambient conditions without requiring cooling of the solution, allows formulation and filling on a production scale over a 24-hour period, and provides longer shelf-life of the lyophilized product at ambient temperature. Ex. 1009 ¶ 45 (citing Ex. 1007, 117, 118). Teagarden predicts that “[t]his type of effect would be expected to be observed for many other drug products which are degraded in the presence of water.” Id. ¶ 46 (citing Ex. 1007, 117).

Based on the current record, we are persuaded that an ordinary artisan, motivated to improve the stability of Ribomustin®, would have looked to Teagarden’s teaching of the benefits of TBA. In addition, as noted by Petitioner, during prosecution of the ’190 patent, the applicants stated that Ribomustin® was “historically lyophilized from a solution of ethanol, water, mannitol, and bendamustine.” Pet. 26 (citing Ex. 1005, 367). Thus, Petitioner argues, based on the teachings of Teagarden, it would have been obvious to substitute ethanol with TBA. Id. Patent Owner now disputes its own statement that Ribomustin® was lyophilized from an ethanol solution as “lacking support.” Prelim. Resp. 19. We are not persuaded based on the record before us.
During prosecution, the applicants argued to the examiner that lyophilizing bendamustine from a TBA solution as claimed would avoid the formation of bendamustine ethyl ester, a degradation product formed when bendamustine was lyophilized from an ethanol solution. Ex. 1005, 367. Based on such representation, the examiner allowed the challenged claims despite concluding that the prior art suggested “using a combination of mannitol and tertiary-butyl alcohol with bendamustine to produce a formulation to be lyophilized.” Id. at 593. The examiner reasoned that the applicants “unexpectedly” found that using TBA led to “no more than 0.5% formation of bendamustine ethyl ester.” Id. Patent Owner may not, after obtaining the challenged patent based on that assertion, take an inconsistent position without presenting persuasive evidence. See New Hampshire v. Maine, 532 U.S. 742, 749 (2001) (explaining that “absent any good explanation, a party should not be allowed to gain an advantage by litigation on one theory, and then seek an inconsistent advantage by pursuing an incompatible theory”).

Based on the current record, we find Patent Owner’s other arguments similarly unpersuasive. For example, Patent Owner contends that Teagarden teaches several co-solvent systems and Petitioner does not show why a skilled artisan would have chosen TBA. Prelim. Resp. 27. In fact, even though Teagarden lists the properties of other solvents, it discusses TBA in detail, gives specific examples of formulations using TBA, and identifies TBA as advantageous over other solvents. Ex. 1007, in passim. Patent Owner also argues that “the possible approaches to solving the bendamustine problem were not known or finite.” Prelim. Resp. 27. This
attorney argument, unsupported by sufficient evidence, is not entitled to much weight.

Patent Owner further asserts that the co-solvent systems “can cause a multitude of problems” and thus, using TBA in the pre-lyophilization formulation is unpredictable. *Id.* at 27–30. Specifically, according to Patent Owner, Teagarden warns that lyophilizing a TBA-containing formulation may cause dried powder near the neck of a vial, which “is not desired because of both a poor appearance and the possibility of negatively impacting the seal with the rubber closure.” *Id.* at 29 (citing Ex. 1007, 119). In addition, when using TBA, “both formulation and process control required optimization to maximize drying rates and to minimize residual solvent levels at the end of drying.” *Id.* (citing Ex. 1007, Abstract, emphasis added by Patent Owner). These “multitude of problems,” Patent Owner argues, “would discourage any formulator from using TBA because of the unpredictability of the results.” *Id.* We are not persuaded.

First, the appearance and the seal with the rubber closure are not a part of any challenged claims. Nor do we consider them, based on the current record, to lead to unpredictability in the obviousness analysis. Second, obviousness does not require absolute predictability of success. *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Instead, for obviousness, all that is required is a reasonable expectation of success. *Id.* at 904. We are persuaded that the combination of the Rote Liste and Teagarden teaches all the limitations required in claim 1, i.e., bendamustine HCl, mannitol, TBA, and water. Optimization of the formulation flows from the “normal desire of scientists or artisans to improve upon what is already generally known.” *In
re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Patent Owner points to no persuasive evidence indicating that the optimization was anything other than the exercise of ordinary skill in the art.

Patent Owner also contends that objective indicia demonstrate the claimed invention would not have been obvious. Prelim. Resp. 34–37. We are not persuaded based on the current record.

For objective evidence of secondary considerations to be accorded substantial weight, Patent Owner must establish a nexus between the evidence and the merits of the claimed invention. Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010). Patent Owner emphasizes that the inventive aspect of the challenged claims lies in using TBA in the pre-lyophilization formulation. Prelim. Resp. 11–13. TREANDA®, which Patent Owner alleges as using the formulation of the ’190 patent (Prelim. Resp. 14), however, does not include TBA. See Ex. 2001, 5 (showing bendamustine HCl, Propylene Glycol, USP, and N,N-Dimethylacetamide, EP as ingredients in TREANDA® Injection, and bendamustine HCl and mannitol as ingredients in TREANDA® for Injection). As a result, Patent Owner has not established sufficiently a nexus between the addition of TBA, and the regulatory approval, the alleged acclaim and copying by others, as well as the asserted commercial success, of TREANDA®.

Patent Owner argues that “adding TBA to the bendamustine/mannitol composition produced a variety of unexpected and desirable results,” such as improved bendamustine stability and fewer impurities. Prelim. Resp. 37. Patent Owner cites the ’190 patent as support. Id. (citing Ex. 1001, 30:9–22, Figs. 2–4). We are not persuaded.
In the ’190 patent, the passage Patent Owner relies on discloses that “the effect of *alcohols* on bendamustine stability is unique, unexpected and useful in manufacturing bendamustine with fewer impurities since an aqueous solution can be used while maintaining the stability of bendamustine.” Ex. 1001, 30:10–14 (emphasis added). In other words, the unexpected results Patent Owner underlines do not appear to be unique to TBA. *See id.* at 30:15–16 (“*All alcohols* at 30% (v/v) reduced the formation of impurities HP1 and Dimer at 5° C. for up to 24 hours.”) (emphasis added). The ’190 patent does state that “TBA was found to be the best stabilizer” of the six alcohols tested. *Id.* at 30:14–15. Teagarden, however, specifically identifies improved stability of both pre-lyophilization solutions and lyophilized products as the advantages of using TBA over other solvents. Ex. 1007, 117–18, 123. Therefore, based on the current record, Patent Owner’s objective indicia do not persuade us not to institute a trial.

In sum, based on the current record, we conclude Petitioner has established a reasonable likelihood it would prevail in showing that claim 1 would have been obvious over the Rote Liste and Teagarden.

**Claims 2 and 3**

Claim 2 depends from claim 1 and recites concentration ranges of bendamustine/bendamustine HCl (12 to 17 mg/ml), mannitol (20–30 mg/ml) and TBA (10–50% (v/v)). Claim 3 depends from claim 2 and recites specific concentrations of bendamustine/bendamustine HCl (15 mg/ml), mannitol (25.5 mg/ml), and TBA (30% (v/v)).
Citing the Declaration of Dr. Suryanarayanan, Petitioner argues that “[i]t would have been obvious to one of ordinary skill in the art that the amounts disclosed in the Rote Liste of bendamustine HCl and mannitol can readily be achieved by pre-lyophilization concentrations that fall within the ranges recited in claim 2.” Pet. 27 (citing Ex. 1002 ¶ 75) (emphasis added). Petitioner also asserts that it would have been “obvious to modify the amounts of bendamustine hydrochloride and mannitol disclosed in the Rote Liste to arrive at the concentrations recited in claim 3 as a matter of routine product optimization.” Id. at 27–28.

We disagree with Petitioner’s reasoning, as it is based on a hindsight approach. Petitioner does not either identify disclosure in the prior art or explain the general knowledge of a skilled artisan that would have suggested the concentrations of the pre-lyophilized ingredients recited in claim 2.

Instead, Dr. Suryanarayanan states:

For example, a bendamustine hydrochloride concentration of about 16.7 mg/ml and a mannitol concentration of 20.0 mg/ml, which both fall in the range of concentrations recited in claim 2, could be used in a pre-lyophilization volume of 1.5 ml. Lyophilization of this volume would result in dry amounts of about 25 mg of bendamustine hydrochloride and 30 mg of mannitol, as recited in the Rote Liste.

Ex. 1002 ¶ 75 (emphasis added). Dr. Suryanarayanan, however, does not explain, without the knowledge of the recited concentrations, why a skilled artisan would have picked a pre-lyophilization volume of 1.5 ml.

Indeed, one of ordinary skill in the art could have used 1 ml (with 25 mg/ml bendamustine HCl and 30 mg/ml mannitol), 2 ml (with 12.5 mg/ml bendamustine HCl and 15 mg/ml mannitol), or 3 ml (with
8.33 mg/ml bendamustine HCl and 10 mg/ml mannitol) pre-lyophilization solution. Lyophilization of each solution would result in dry compositions in the amounts recited in the Rote Liste. But in all of those solutions, either or both of bendamustine HCl and mannitol concentrations would fall outside the recited ranges. Petitioner does not explain adequately why an ordinary artisan would have selected a composition with bendamustine HCl and mannitol in concentrations within the recited ranges. We, thus, conclude Petitioner has not established a reasonable likelihood it would prevail in showing that claims 2 and 3 would have been obvious over the Rote Liste and Teagarden.

Claim 4

Claim 4 recites “[a] lyophilized pharmaceutical composition made from the pharmaceutical composition according to claim 1.”

Claim 4, a product-by-process claim, is directed to the freeze-dried powder comprising bendamustine HCl and mannitol. See Ex. 2001, 5 (showing TREANDA for injection is supplied as lyophilized powder of bendamustine HCl and mannitol); see also Prelim. Resp. 14 (asserting that TREANDA uses the formulation of the ’190 patent). In determining the patentability of the product-by-process claim here, we focus on the product and not the process of making it. See Amgen Inc. v. F. Hoffman–La Roche Ltd., 580 F.3d 1340, 1369 (Fed. Cir. 2009). “If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985).
The Rote Liste discloses a dry substance comprising bendamustine HCl and mannitol. Ex. 1006, 8. Petitioner contends that the composition disclosed in the Rote Liste was produced from lyophilizing a liquid solution. *Id.* at 28 (citing Ex. 1005, 367). Petitioner also asserts that Teagarden teaches using TBA in formulations intended for lyophilization. *Id.*

According to Petitioner, it would have been obvious to one of ordinary skill in the art, “having already combined the teachings of the Rote Liste and Teagarden to arrive at the composition of claim 1 . . . to lyophilize the composition using standard freeze-drying techniques that were known in the art . . . thereby arrive at the lyophilized pharmaceutical composition of claim 4.” Pet. 28–29 (internal citations omitted).

Based on the current record, we find Petitioner’s arguments persuasive. Thus, we conclude Petitioner has established a reasonable likelihood it would prevail in showing that claim 4 would have been obvious over the Rote Liste and Teagarden.

**Claims 5, 6, 8, and 9**

Claim 5 depends from claim 4 and further recites the concentration ranges of bendamustine HCl, mannitol, and TBA. Claim 6 depends from claim 5 and recites specific concentrations of bendamustine HCl, mannitol, and TBA. Claims 8 and 9 depend from claims 5 and 6, respectively, and further require the lyophilized pharmaceutical composition to “contain[] not more than about 0.5% bendamustine ethylester.”

Petitioner’s argument regarding the obviousness of claims 5 and 6 over the combination of the Rote Liste and Teagarden, in its entirety, reads:
The ranges and concentrations recited in claims 5 and 6 are identical to those recited in claims 2 and 3, and would have been obvious to a person of ordinary skill in the art prior to January 14, 2005 for the reasons explained above with respect to claims 2 and 3.

Pet. 29. As explained above, Petitioner has not established a reasonable likelihood it would prevail in showing that claims 2 and 3 would have been obvious over the Rote Liste and Teagarden. Thus, we similarly conclude Petitioner has not established a reasonable likelihood it would prevail in showing that claims 5 and 6, as well as their dependent claims, claims 8 and 9, would have been obvious over the Rote Liste and Teagarden.

Claim 7

Claim 7 depends from claim 4 and further requires the lyophilized pharmaceutical composition to “contain[] not more than about 0.5% bendamustine ethylester.” Referring to Table 13 of the ’190 patent, Petitioner argues that even though Ribomustin® was lyophilized from an ethanol solution, it “contained less than 0.5% bendamustine ethylester.” Id. Thus, according to Petitioner, it would have been obvious to a skilled artisan that substituting ethanol with TBA in the pre-lyophilization solution would not lead to the formation of additional bendamustine ethylester, because, as acknowledged by Patent Owner, bendamustine ethylester is formed only by reaction of bendamustine with ethanol. Id. at 30–31. Based on the current record, we find Petitioner’s argument persuasive. Thus, we conclude Petitioner has established a reasonable likelihood it would prevail in
showing that claim 7 would have been obvious over the Rote Liste and Teagarden.

**Obviousness over the Rote Liste, Teagarden, and Nuijen**

Petitioner asserts that claims 1–9 would have been obvious over the Rote Liste, Teagarden, and Nuijen. Pet. 34–48. For purposes of this Decision, we assume, without deciding, that one of ordinary skill in the art would have had a reason to combine the teachings of the Rote Liste, Teagarden, and Nuijen.

As explained above, we institute a review of obviousness of claims 1, 4, and 7 over the Rote Liste and Teagarden. Thus, we exercise our discretion and do not institute a review of obviousness of these claims over the Rote Liste, Teagarden, and Nuijen.

For claims 2, 3, 5, 6, 8, and 9, based on the current record, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in this assertion regarding those claims.

According to Petitioner, Nuijen teaches “the combination of mannitol, TBA, water and drug, in a pre-lyophilization formulation” for aplidine, an anti-tumor drug. *Id.* at 36–37. Specifically, Nuijen teaches that “[a] formulation solution consisting of 500 μg/mL aplidine and 25 mg/mL D-mannitol as bulking agent in 40% (v/v) tert-butanol/water was selected for the lyophilization of aplidine.” *Id.* at 37 (citing Ex. 1008, 203). Petitioner asserts that the concentrations of both mannitol and TBA are within the ranges recited in claim 2. *Id.* at 40–41. Regarding the concentration range of bendamustine HCl recited in claim 2, Petitioner argues that it would have
been obvious to one of ordinary skill in the art that the amounts of bendamustine and mannitol disclosed in the Rote Liste “can be readily achieved by pre-lyophilization concentrations that fall within [the] ranges . . . recited in claim 2.” Id. at 40. As explained above, we are not persuaded by this argument. See supra at 17.

Petitioner contends that a skilled artisan would have been motivated to optimize the concentrations of bendamustine HCl, mannitol, and TBA to arrive at the concentrations recited in claim 3. Id. at 41. Even if we were to apply this argument to both claims 2 and 3, we would not be persuaded. Nuijen teaches using 25 mg/mL mannitol in the pre-lyophilization solution. Ex. 1008, 203. Combining this teaching with that of the Rote Liste, i.e., the ratio of bendamustine HCl/mannitol is 25/30 (see Ex. 1006, 8), the concentration of bendamustine HCl would have been over 20.8 mg/ml (25x25/30 mg/ml), outside the range recited in claim 2 and different from the concentration recited in claim 3. Petitioner does not point to sufficient evidence, be it a prior art teaching or knowledge in the art, to suggest the need to modify the concentration of bendamustine HCl from 20.8 mg/ml to 12–17 mg/ml and 15 mg/ml, as recited in claims 2 and 3, respectively.

We, thus, conclude Petitioner has not established a reasonable likelihood it would prevail in showing that claims 2 and 3 would have been obvious over the Rote Liste, Teagarden, and Nuijen.

Petitioner’s argument regarding the obviousness of claims 5 and 6 over the combination of the Rote Liste, Teagarden, and Nuijen is entirely based on its argument regarding the obviousness of claims 2 and 3. Thus, we similarly conclude Petitioner has not established a reasonable likelihood
it would prevail in showing that claims 5 and 6, as well as their dependent claims, claims 8 and 9, would have been obvious over the Rote Liste, Teagarden, and Nuijen.

**Obviousness Over the Rote Liste, Teagarden, Nuijen, and Gust**

Petitioner further argues that claims 7–9 would have been obvious over the Rote Liste, Teagarden, Nuijen, and Gust. Pet. 48–52. For purposes of this Decision, we assume, without deciding, that one of ordinary skill in the art would have had a reason to combine the teachings of the Rote Liste, Teagarden, Nuijen, and Gust.

As explained above, we institute a review of obviousness of claim 7 over the Rote Liste and Teagarden. Thus, we exercise our discretion and do not institute a review of obviousness of this claim over the Rote Liste, Teagarden, Nuijen, and Gust.

For claims 8 and 9, 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. 49–50 (citing Ex. 1009, 293, 298, 299). In other words, Gust does not remedy the deficiencies of the Rote Liste, Teagarden, and Nuijen, 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 claims 8 and 9 would have been obvious over the Rote Liste, Teagarden, Nuijen, and Gust.
Anticipation of claims 4, 5, 7, and 8 by the Rote Liste

Petitioner argues that the Rote Liste anticipates claims 4, 5, 7, and 8. Pet. 52–58. Based on the current record, we determine that Petitioner has shown a reasonable likelihood that it would prevail in this assertion with regard to claims 4 and 7, but not claims 5 and 8.

Claims 4 and 7

Claim 4 and its dependent claims, claims 5, 7, and 8, are product-by-process claims. See supra at 5–6. A product-by-process claim “can be anticipated by a prior art product that does not adhere to the claim’s process limitation.” Amgen, 580 F.3d at 1370. But, if the process by which the product is made imparts “structural and functional differences” distinguishing the claimed product from the prior art, then those differences “are relevant as evidence of no anticipation” although they “are not explicitly part of the claim.” Id.

Petitioner contends that “after lyophilizing the pharmaceutical composition of claim 1, the resulting product disclosed in claim 4 contains solid bendamustine or bendamustine hydrochloride and mannitol; the tertiary-butyl alcohol and water have been removed by the lyophilizing step.” Pet. 55. The Rote Liste discloses a dry substance comprising bendamustine HCl and mannitol. Ex. 1006, 8. According to Petitioner, because there is no difference between the two products, the Rote Liste anticipates claim 4. Pet. 55.

Patent Owner counters that the lyophilized composition disclosed in the Rote Liste is made from an ethanol solution, whereas claim 4 is directed to a composition made from a TBA solution. Prelim. Resp. 40. According
to Patent Owner, features of a lyophilized composition made using ethanol are “demonstrably different” from a lyophilized pharmaceutical composition made using TBA. *Id.* at 40. Based on the current record, we are not persuaded.

Patent Owner cites two excerpts of the ’190 patent for support. *Id.* First, the ’190 patent discloses that “[l]yophilates produced with 30% (v/v) TBA according to the invention reconstitute within 3-10 minutes as compare[d] to commercially available Ribomustin which may take 30-45 minutes.” Ex. 1001, 31:39–42. Second, the ’190 patent discloses that “[t]he lyophilized vials filled from solutions of 10% ethanol [and] 20% ethanol . . . produced either a collapsed cake or a film residue. The only solvent system producing an acceptable cake was 30% TBA.” *Id.* at 31:6–10. Both sentences stress the importance of 30% TBA. Claim 4, however, does not specify any concentration of TBA. Thus, based on the current record, we are not persuaded that the features of the composition of claim 4 differ from those of the composition disclosed in the Rote Liste. We conclude Petitioner has established a reasonable likelihood it would prevail in showing that the Rote Liste anticipates claim 4.

For claim 7, Petitioner refers to Table 13 of the ’190 patent and argues that “Ribomustin® inherently contains less than 0.5% bendamustine ethylester.” *Id.* at 57. As a result, Petitioner contends, the Rote Liste anticipates claim 7. Based on the current record, we find Petitioner’s argument persuasive. Thus, we conclude Petitioner has established a reasonable likelihood it would prevail in showing that the Rote Liste anticipates claim 7.
Claims 5 and 8

Petitioner further asserts that “[t]he dry pharmaceutical composition of 25 mg of bendamustine hydrochloride and 30 mg of mannitol described in the Rote Liste anticipates the lyophilized product recited in claim 5.” *Id.* at 56. Based on the current record, we are not persuaded.

Anticipation requires disclosure of each and every claim limitation in a single prior art reference, either explicitly or inherently. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). The Rote Liste does not expressly disclose the concentrations of bendamustine HCl and mannitol as recited in claim 5. Petitioner, therefore, must demonstrate that the concentrations of bendamustine HCl and mannitol are “necessarily present, or inherent,” in the Rote Liste. *Id.* at 1377. “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.” *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

The Rote Liste discloses a dry pharmaceutical composition of 25 mg of bendamustine hydrochloride and 30 mg of mannitol. Ex. 1006, 8. Petitioner argues that, lyophilizing 1.5 ml solution of 16.7 mg/ml bendamustine HCl and 20 mg/ml mannitol, as recited in claim 5, produces the amounts disclosed in the Rote Liste. Pet. 56. But, lyophilizing 3 ml solution of 8.3 mg/ml bendamustine HCl and 10 mg/ml mannitol also produces the amounts disclosed in the Rote Liste. Yet, neither concentration falls within the ranges recited in claim 5. In other words, the composition
disclosed in the Rote Liste is not necessarily lyophilized from a solution with the concentrations of bendamustine HCl and mannitol recited in claim 5. Conversely, lyophilizing 1 ml solution of 16.7 mg/ml bendamustine HCl and 20 mg/ml mannitol, as recited in claim 5, does not produce the amounts disclosed in the Rote Liste. In other words, lyophilizing a solution with the concentrations of bendamustine HCl and mannitol recited in claim 5 does not necessarily result in the composition disclosed in the Rote Liste. Thus, based on the current record, we conclude Petitioner has not established a reasonable likelihood it would prevail in showing that the Rote Liste anticipates claim 5 and its dependent claim, claim 8.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1, 4, and 7 of the ’190 patent. The information presented in the Petition and accompanying evidence, however, does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 2, 3, 5, 6, 8, and 9 of the ’190 patent.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an inter partes review is hereby instituted on the following grounds:
1. claims 1, 4, and 7 as obvious over the Rote Liste and Teagarden; and

2. claims 4 and 7 as anticipated by the Rote Liste;

FURTHER ORDERED that no other ground of unpatentability is authorized in this inter partes review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), inter partes review of the ’190 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.
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