UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AGILA SPECIALTIES INC. and MYLAN LABORATORIES LIMITED,

Petitioners

v.

CEPHALON, INC.

Patent Owner

Case No. IPR2015-00503
Patent No. 8,436,190

CEPHALON, INC.'S PRELIMINARY PATENT OWNER RESPONSE

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I. INTRODUCTION

Patent Owner Cephalon Inc.'s ("Cephalon's") U.S. Patent No. 8,436,190 ("the '190 Patent") claims a new bendamustine composition used to treat cancers such as non-Hodgkin lymphoma ("NHL") and chronic lymphocytic leukemia ("CLL"). Doctors and patients have hailed Cephalon's invention as a leap forward over prior chemotherapy drugs, and Cephalon's TREANDA® product for injection has been a huge commercial success. Agila Specialties Inc. and Mylan Laboratories Limited (referred to collectively as "Agila") nonetheless petition to invalidate Cephalon's patent in view of nothing more than a rehashing of prior art teachings that were before the Examiner during prosecution of the claims at issue. But Agila fails to demonstrate there is a reasonable likelihood it will prevail regarding at least one of the claims it challenges in the petition, for at least the following reasons:

First, Agila's primary reference – the "Rote Liste" – is a German drug index that merely discloses a dry substance containing bendamustine hydrochloride and mannitol, marketed as RIBOMUSTIN®. (Ex. 1006.) Independent claim 1 of the '190 Patent, however, recites a composition of bendamustine or bendamustine hydrochloride, mannitol, ***tertiary-butyl alcohol ("TBA") and water***. The remaining claims that Agila challenges all depend from claim 1. During prosecution of the '190 Patent, RIBOMUSTIN® was discussed ***at length***, not only

in the '190 Patent specification but also in several references considered by the Examiner. *See*, *e.g.*, Ex. 1001, 1:50-65 ("[t]he current lyophilized formulation of bendamustine (Ribomustin®) contains bendamustine hydrochloride and mannitol in a sterile lyophilized form as a white powder for intravenous use following reconstitution."); *see also* 2:44-48. Despite these detailed disclosures, the Examiner did not find that RIBOMUSTIN® defeated the patentability of the claims, alone or in combination with any other references disclosed during prosecution, including the teachings of Teagarden. *Id.* at 2:60-62 ("Teagarden *et al.* disclose[s] lyophilized formulations of prostaglandin E-1 made by dissolving PGE-1 in a solution of lactose and tertiary butyl alcohol (U.S. Patent No. 5,770,230).")[1] This is reason enough to reject Agila's petition. 35 U.S.C. § 325(d) (allowing the Board to reject a petition where the "same or substantially the same prior art… previously w[as] presented to the Office.") But if the Board is inclined to review the art anew, the only possible conclusion is that the Rote Liste (alone or

[1] In its Petition, Agila relies upon a Teagarden review article titled "Practical Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems," *Eur. J. Pharmaceut. Sci.* (Ex. 2007). The Teagarden patent disclosed and described in the '190 Patent's specification contains essentially the same teachings concerning TBA as the article relied upon by Agila.

in combination) neither anticipates nor renders obvious the challenged claims of the '190 Patent.

Agila readily admits that a combination of bendamustine, mannitol, TBA, and water is not disclosed in the Rote Liste. (Petition at 8.) Agila nonetheless erroneously argues that the Rote Liste ***anticipates*** dependent claims 4, 5, 7, and 8 (Ground 4) through a tortured claim construction that ignores the fact these dependent claims explicitly recite pharmaceutical compositions made from ***the composition of claim 1***. That claim 1 requires a composition having TBA and water cannot be disregarded. The Rote Liste thus cannot anticipate the claims and Agila's Ground 4 must be rejected.

Agila's one and only articulated motivation to combine the Rote Liste with Teagarden (Ground 1) plus the Nuijen and Gust references (Grounds 2 and 3) is "to gain the many benefits of using TBA" for "a water unstable drug, such as bendamustine." (Petition at 24.) But this "problem" was first identified (and then solved) ***by the inventors of the '190 Patent***. Agila acknowledges that bendamustine compositions like RIBOMUSTIN® were marketed in Germany for more than ***forty years***. (Ex. 1001 at 1:50-57.) Yet ***not one*** of the many references cited by Agila in its Petition identifies any deficiency in bendamustine products over the decades or even the alleged "motivation" that Agila claims would have prompted the combination. Unable to rely on objective evidence, Agila's petition

resorts to imbuing one of ordinary skill in the art with knowledge of the '190 Patent, when no prior art reference of record conveys or suggests that knowledge. This is nothing more than "the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). The claimed invention of the '190 Patent cannot be used as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

Second, Agila's references would not have predictably led one of ordinary skill in the art to a bendamustine/mannitol/TBA/water composition. Insofar as TBA was known, it was merely one of an almost limitless number of co-solvent combinations, and thus not the predictable choice. As for Teagarden, it discusses numerous organic solvents in the context of the lyophilization of five drugs, including prostaglandin E1. Agila's petition utterly fails to address the significant structural and physico-chemical differences between these drugs and bendamustine or the impact of these differences on drug stability or reconstitution time. It thus fails to demonstrate that the suggested modification of RIBOMUSTIN® would predictably produce the claimed invention.

In fact, Teagarden repeatedly emphasizes the unpredictable nature of formulation development. Ex. 1007 at 115-116 ("The development scientist must

be aware that use of these organic/water co-solvent systems ***can cause a multitude of problems***…," (emphasis added)); 131 ("The practicalities of use of these co-solvent systems must be properly assessed ***before they should be considered for use***. This especially applies when using them in the manufacturing" of a pharmaceutical injectable product, (emphasis added)).

For all of these reasons and those detailed below, Ground 1 must be rejected. Neither Nuijen nor Gust – both inapposite here – remedy the deficiencies of the Rote Liste in view of Teagarden. Accordingly, Grounds 2 and 3 must be rejected as well.

Third, the objective indicia demonstrate the '190 Patent's inventiveness. The patent specification shows the unexpected results of exceptional stability, ease of manufacturing, and ease of reconstitution. Furthermore, doctors, patients, regulators, and cancer advocacy groups have all praised TREANDA® as a significantly improved cancer treatment. TREANDA® has accordingly been a major success, with sales routinely beating market expectations. Additionally, many competitors such as Agila and Mylan are copying the invention. The '190 Patent cannot be deemed obvious in these circumstances—if it were, then others surely would have brought an improved bendamustine/mannitol/TBA/water composition drug to market decades sooner than Cephalon.

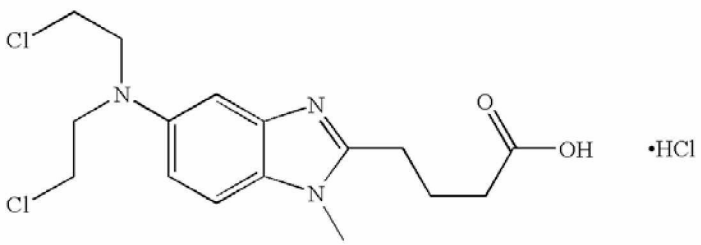
Fourth, and finally, Agila's Petition violates the Board's rules concerning redundant and duplicative arguments.

For these reasons and those set forth in detail below, Cephalon respectfully requests that the Board deny Agila's petition.

II. THE '190 PATENT

The invention of the '190 Patent pertains to the field of pharmaceutical compositions for the treatment of various diseases, especially neoplastic diseases and autoimmune diseases. (Ex. 1001 at 1:6-11.) The challenged claims recite pharmaceutical formulations comprising nitrogen mustards, particularly the nitrogen mustard bendamustine or bendamustine HCl. Bendamustine (4-{5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolyl}butyric acid, is an atypical structure with a benzimidazole ring, whose structure includes an active nitrogen mustard (*see* Formula I, which shows bendamustine hydrochloride):

Formula I



(*Id.* at 1:33-49.)

Bendamustine was initially synthesized in 1963 in Germany and was available from 1971 to 1992 under the name CYTOSTASAN®. (*Id.* at 1:50-52.) Since that time, it has been marketed in Germany under the trade name

RIBOMUSTIN®. (*Id.* at 1:53-54.) Prior to the inventions of the '190 Patent, bendamustine compositions were widely used in Germany to treat CLL, Hodgkin's disease, NHL, multiple myeloma, and breast cancer (*id.* at 1:54-57), but never were approved for sale or use in the United States.

Bendamustine is supplied as a lyophilized (freeze-dried) product. RIBOMUSTIN® (which the specification discloses contains bendamustine hydrochloride and mannitol in a sterile lyophilized form as a white powder for intravenous use following reconstitution) is unstable when exposed to light. (*Id.* at 1:60-65.) Therefore, the product is stored in brown or amber-colored glass bottles. (*Id.*) The inventors of the '190 Patent discovered that the lyophilized formulation of bendamustine contains degradation products or impurities that may occur during manufacturing of the drug substance and/or during the lyophilization process used to make the finished drug product. (*Id.* at 1:65-2:2.)

The '190 Patent specification also teaches that bendamustine is formulated as a lyophilized powder for injection with 100 mg of drug per 50 mL vial or 25 mg of drug per 20 mL vial. The vials are opened and reconstituted as close to the time of patient administration as possible. The product is reconstituted with 40 mL (for the 100 mg presentation) or 10 mL (for the 25 mg presentation) of sterile water for injection. The reconstituted product is further diluted into 500 mL, q.s., 0.9%

Sodium Chloride for Injection. The route of administration is by intravenous infusion over 30 to 60 minutes. (*Id.* at 2:3-12.)

The inventors observed that reconstitution of bendamustine lyophilized powder is difficult. (*Id.* at 2:20-21.) Reports from the clinic indicated that reconstitution can require at least fifteen minutes and may require as long as thirty minutes. (*Id.* at 2:21-23.) Besides being burdensome and time-consuming for the healthcare professional responsible for reconstituting the product, the inventors realized that lengthy exposure of bendamustine to water during the reconstitution process increased the potential for loss of potency and impurity formation due to the hydrolysis of the bendamustine product by water. (*Id.* at 23-28.)

The inventors thus identified "a need for lyophilized formulations of bendamustine that are easier to reconstitute and which have a better impurity profile than the current lyophilate (lyophilized powder) formulations of bendamustine." In other words, there was a need for an improvement over the RIBOMUSTIN® product described in the Rote Liste that was available at the time of the invention. (*Id.* at 2:29-32.)

The inventors of the '190 Patent began experimenting to determine if it was possible to prepare formulations that were easier to reconstitute and that had "a better impurity profile than Ribomustin®" with respect to impurities, including hydroxyl-chloro ("HP1"), bendamustine dimer, and bendamustine ethylester, prior

to reconstitution, upon storage of the lyophilate, or following reconstitution and admixture. (*Id.* at 20:24-42.)

The results of their experiments indicated that the stability of bendamustine HCl with respect to HP1 and dimer improves with increasing alcohol concentration. (*Id.* at 24:47-49; Figs. 2-4.) The results further indicated 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 the bendamustine." (*Id.* at 30:9-22.) TBA was found to be the best stabilizer. (*Id.* at 30:14-15; Figs. 2-4.)

A. Cephalon's Invention and Patent

The inventors further discovered that since the concentration of bendamustine is higher in a 30% TBA/water saturated solution as compared with other alcohol solutions, the vial size required to fill 100 mg of bendamustine could be decreased from the RIBOMUSTIN® presentation. (*Id.*)

Mannitol was selected as a bulking agent "in order to maintain a formulation similar to RIBOMUSTIN®." (*Id.* 30:47-61.) The inventors conducted studies to evaluate the effect of mannitol on bendamustine solubility and the appearance of the product. They discovered that mannitol decreased the solubility of bendamustine (at 15 mg/mL) in both ethanol and TBA aqueous solutions. (*Id.*) For example, solutions containing 5% and 10% ethanol and TBA without mannitol

did not precipitate over 24 hours. However, for samples with mannitol, precipitate was observed within 24 hours. There was no precipitate with aqueous solutions containing 30% (v/v) TBA, 15 mg/mL bendamustine, and 25.5 mg/mL mannitol. (*Id.*)

The inventors learned that all of the alcohols they tested increased the stability and solubility of bendamustine. (*Id.* at 30:62-31:12.) However, a significant mole fraction was required to affect the stability of the filling solution and the ease of manufacturing. (*Id.*) Smaller alcohols had the undesirable effect of lowering the freezing point of the bulk solution and thus requiring long lyophilization cycles at lower temperatures. Higher concentrations of methanol and ethanol produced unattractive cakes that were difficult to reconstitute. The inventors prepared and lyophilized 10% ethanol, 20% ethanol, 10% iso-propanol, 20% iso-propanol, or 30% TBA aqueous solutions containing bendamustine (15 mg/mL), and mannitol (25.5 mg/mL). They learned that lyophilized vials filled from solutions of 10% ethanol, 20% ethanol, 10% iso-propanol, 20% iso-propanol produced either a collapsed cake or a film residue. (*Id.*) Additionally, reconstitution of 10% ethanol, 20% ethanol, 10% iso-propanol, 20% iso-propanol lyophilized vials were difficult and did not fully dissolve until >45 minutes. (*Id.*) The 30% TBA solvent system produced an acceptable cake. (*Id.* at 31:8-12.)

The inventors theorized that the problems associated with RIBOMUSTIN® reconstitution may be associated with precipitation caused by melt back (presence and evaporation of a liquid) during lyophilization. (*Id.* at 31:25-42.) The inventors further identified a solution to this problem based on the use of TBA. (*Id.*) Indeed, the inventors discovered that lyophilates produced with 30% (v/v) TBA according to the invention reconstituted within 3-10 minutes as compared to RIBOMUSTIN®, which may take 30-45 minutes. (*Id.*)

With an effective priority date of January 14, 2005, Cephalon filed for a patent on its invention. During prosecution, the Examiner concluded that:

> [T]he prior art teaches a formulation of bendamustine and mannitol to be lyophilized. The prior art also teach[es that] a combination of mannitol, tertiary-butyl alcohol, water, and an anti-neoplastic agent can be lyophilized. The prior art suggests using a combination of mannitol and tertiary-butyl alcohol with bendamustine to produce a formulation to be lyophilized. ***However, Applicant has unexpectedly found that the addition of tertiary-butyl alcohol stabilizes the formulation such that bendamustine degradation is negligible (no more than 0.5% formation of bendamustine ethyl ester).***

(Ex. 1005 at Notice of Allowability dated February 4, 2013 at 2, emphasis added.) The Examiner thus allowed the '190 Patent's claims over the art of record.

The PTO accordingly issued the '190 Patent on May 7, 2013. It has 9 claims—one independent claim (1), and 8 dependent claims.

The independent claim is for a "[a] pharmaceutical composition comprising bendamustine or bendamustine hydrochloride, mannitol, tertiary-butyl alcohol and water." Claims 2 and 3 specify concentrations of bendamustine, mannitol, and TBA. Claim 4 claims "[a] lyophilized pharmaceutical composition made from the pharmaceutical composition according to claim 1." Claims 5-6 depend from claim 4 and specify concentrations of bendamustine, mannitol, and TBA. Claims 7, 8 and 9 depend from claim 4, 5, and 6, respectively, and specify that the composition contains not more than about 0.5% bendamustine ethylester. (*See* Ex. 1001, 34:19-60.)

B. Regulatory Approval and Market Response

The FDA approved TREANDA® in March 2008, before the PTO issued the '190 Patent. As shown in the prescribing information, bendamustine is TREANDA®'s active ingredient, and mannitol is an excipient. (TREANDA® Prescribing Information, Ex. 2001.) TREANDA® thus uses Cephalon's formulation under the '190 Patent.

The drug also won U.S. approval seven months later as a second (or later) line therapy for patients with the indolent or slow-growing form of NHL. (*Id.*) A trial with more than 500 patients showed TREANDA® delayed cancer growth for 55 months, compared with 35 months for those taking the standard regimen. After a median observation time of 32 months, 40% of the TREANDA®-treated patients

had the disease completely disappear, compared with 31% on the older therapy. TREANDA® also had fewer infections and less hair loss than the standard therapy, the research found. ("Cephalon's Treanda Poised for 10-Fold Sales Surge," *Bloomberg*, Ex. 2002.) In another clinical trial related to CLL, TREANDA® was compared to chlorambucil (another drug approved by the Food and Drug Administration). (Ex. 2003.) Both medications were given without any other chemotherapy agents. There were 153 patients who took TREANDA®, and 148 patients who took chlorambucil. TREANDA® provided a higher overall response rate vs. chlorambucil. (*Id.*) In fact, 59% of patients responded to TREANDA® and 26% of patients responded to chlorambucil. (*Id.*) TREANDA® has also been granted orphan drug status by the FDA for the treatment of CLL and NHL.

The response to TREANDA® has been extraordinary, and doctors have been impressed. "It's basically a homerun – not only was it less toxic, but it was more efficacious," said Richard Van Etten, director of the Tufts Medical Center Cancer Center in Boston. (Ex. 2002.) "It is potentially practice-changing." (*Id.*) Indeed, "CHOP[2] has been the standard of care for three decades, and this is the

[2] "CHOP" is a short-hand for a chemotherapy drug combination consisting of **c**yclophosphamide, doxorubicin **h**ydrochloride, **o**ncovin, and **p**rednisone.

first ***truly different combination***," said Vincent Picozzi, a hematologist and oncologist at the Virginia Mason Clinic in Seattle, and a scientific committee member at the American Society of Hematology. (*Id.*, emphasis added.) Using TREANDA® instead of the CHOP cocktail in slow-moving NHL treatment could increase the number of U.S. patients taking TREANDA® each year to about 30,000 people, according to investment bank and asset management firm Piper Jaffray. (*Id.*) Dr. Kanti Rai, Chief of Hematology Oncology at Long Island Jewish Medical Center, said: "I am very pleased to learn of the FDA's approval of bendamustine for the treatment of relapsed/refractory indolent lymphomas. As is the case also with CLL, patients suffering from relapsed/refractory indolent lymphoma do not have many options available to them for a treatment regimen which has demonstrated efficacy following a prospectively conducted clinical study. Bendamustine is a welcomed addition to an otherwise depressingly small number of available lists." ("FDA approves bendamustine hydrochloride for NHL," *HemOnc Today*, Nov. 4, 2008, Ex. 2004.)

TREANDA®'s sales performance reflects the enthusiasm. TREANDA® sales in the United States passed $1 billion in 2011 and were reported to be over $3 billion over the last 7 years. ("Cephalon drug Treanda passes $1B in sales," *Philadelphia Business Journal*, Ex. 2005; *see generally* Cephalon Form 10Ks and Teva Pharmaceuticals Industries Limited Form 20-Fs, Exs. 2006-2010.)

III. AGILA'S PETITION

Despite the plaudits and market success, Agila now advances anticipation and obviousness grounds to try to invalidate the '190 Patent because it wishes to infringe the patent.

A. Alleged Grounds of Unpatentability

In its Ground 1, Agila argues the Rote Liste in view of Teagarden renders obvious all of the claims of the '190 Patent under 35 U.S.C. § 103 (Claims 1-9). But Agila concedes that the Rote Liste does not teach TBA and Teagarden does not consider bendamustine. (Petition at 9.) Agila also ignores the fact that the Examiner already determined that Cephalon's claims are patentable over references that describe RIBOMUSTIN® and TBA. Agila further fails to show that a person of ordinary skill would have been motivated to make such a combination or would have had a reasonable expectation of successfully doing so.

In its Ground 2, Agila argues that Nuijen (Ex. 1008) (in combination with the Rote Liste and Teagarden) would have inspired a formulator to use mannitol and TBA when formulating anti-cancer drugs, allegedly rendering claims 1-9 of the '190 Patent obvious under 35 U.S.C. § 103. Nuijen, however, concerns a vastly different drug – aplidine – "a novel representative of an evolving group of anticancer agents derived from marine sources." (Ex. 1008 at 193.) Agila concedes that "Nuijen does not disclose a pre-lyophilization solution of

bendamustine or bendamustine hydrochloride." (Petition at 9.) Agila further wholly fails to address the significant physico-chemical differences between bendamustine and aplidine and their impact on lyophilization, especially stability. Accordingly, Nuijen does not resolve the deficiencies of the Rote Liste and Teagarden.

In Ground 3, Agila argues that Gust (Ex. 1009) (in combination with the Rote Liste, Teagarden, and Nuijen) would have suggested to a formulator that bendamustine hydrolyzes in water and creates degradation products, allegedly rendering claims 7-9 of '190 Patent obvious under 35 U.S.C. § 103. But Agila concedes that Gust does not disclose a lyophilized composition of bendamustine or bendamustine hydrochloride containing not more than about 0.5% bendamustine ethylester as recited in claims 7-9. (Petition at 11.) As a result, Gust does not resolve the deficiencies of the Rote Liste, Teagarden, and Nuijen.

In Ground 4, Agila argues that the Rote Liste anticipates claims 4, 5, 7, and 8. Agila's argument is based on a flawed claim construction that asks the Board to ignore that claims 4, 5, 7, and 8 depend on claim 1, which recites elements (TBA and water) that are indisputably not disclosed in the Rote Liste.

B. Claim Construction

Cephalon reserves its right to address Agila's claim construction proposals and definition of one of ordinary skill in the art in its Patent Owner's Response, if

needed. For purposes of this Preliminary Response, Cephalon only disputes Agila's proposed claim construction of "made from." The remaining claim terms need no construction to determine whether to institute the proceeding.

"Made From." As part of its misguided attempt to convert claims 4, 5, 7, and 8 to product-by-process claims – despite the fact that these claims depend from claim 1, a composition claim – Agila proposes that "made from" means "made from the process of lyophilizing." But the plain meaning of claim 4 and the claims dependent thereon indicates that "made from" refers to the composition of claim 1, not the "process" of lyophilizing. (*See* Ex. 1001, claim 4.) Agila's attempt to insert process steps where there are none should be rejected.

C. Statement of Material Facts

Cephalon does not dispute Agila's material fact 1. Cephalon disputes material facts 2, 3, and 4 as lacking support in the citations provided by Agila.

IV. ARGUMENT

Cephalon respectfully requests that the Board deny Agila's Petition for failing to show a reasonable likelihood of success in proving that the '190 Patent is invalid. 35 U.S.C. § 314(a) (Board "may not authorize an [IPR] to be instituted" unless it determines that 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.").

A patent is invalid only "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is a question of law, based on underlying factual determinations including: "the scope and content of the prior art;" "differences between the prior art and the claims at issue;" and "[s]uch secondary considerations as commercial success…, etc." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

The Petition suffers from multiple deficiencies: (1) Agila's argument relies on prior art teachings substantially the same as those considered in prosecution, and an unreasonable claim construction; (2) Agila's obviousness arguments rely on a hindsight-tainted reconstruction of the claim elements and further do not account for multiple objective indicia of inventiveness; and (3) the Petition violates IPR rules. These deficiencies defeat all of Agila's stated grounds. But if the Board concludes that only certain grounds are defeated, it should not institute a proceeding at least as to those. 37 C.F.R. § 42.108(b) (Board may "deny some or all grounds for unpatentability for some or all of the challenged claims").

A. Grounds 1-3: Agila Fails to Show a Reasonable Likelihood of Proving Obviousness

a. References Describing RIBOMUSTIN® and TBA Were Before the Examiner, Who Did Not Reject the Claims In View of Them

Under 35 U.S.C. § 325(d), "[i]n determining whether to institute [an IPR proceeding], the [Board] 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." Here, Agila primarily relies on the Rote Liste for its obviousness arguments (and exclusively for its anticipation argument, Ground 4, discussed below). As detailed above, the Rote Liste merely discloses RIBOMUSTIN®, which was discussed ***at length*** in the '190 Patent's specification, and was thus squarely before the Examiner during prosecution. *See, e.g.*, Ex.1001 at 1:50-57 ("Bendamustine was initially synthesized in 1963 in the German Democratic Republic (GDR) and was available from 1971 to 1992 in that location under the name Cytostasan®. Since that time, it has been marketed in Germany under the trade name Ribomustin®. It has been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer."); 2:44-48 ("Ribomustin® bendamustine Product monograph (updated January 2002) http://www.ribosepharm.de/pdf/ribomustin_bendamustin/productmonograph.pdf provides information about Ribomustin® including product description."); Fig. 6

(showing a chromatogram for Ribomustin® using HPLC method No. 1); 12:14-18 ("the lyophilized products of the present invention have a better impurity profile than Ribomustin® with respect to certain impurities, in particular HP1, bendamustine dimer, and bendamustine ethylester, prior to reconstitution, upon storage of the lyophilate, or following reconstitution and admixture."); 20:33-42 ("the effect of various alcohols on the degradation of bendamustine was evaluated to determine if formulations could be found that would allow longer fill finish times, provide lyophilate powders that could be reconstituted more quickly than the current Ribomustin® formulation, and/or provide lyophilized preparations of bendamustine with a better impurity profile with respect to certain impurities, e.g., HP1, and BM1 dimer than Ribomustin®."); 21:29-32 ("Other degradants contained in the Ribomustin lyophilized product are bendamustine ethylester (BM1EE) (Formula IV) and BM1DCE (Formula V). BM1EE is formed when bendamustine reacts with ethyl alcohol."); Table 13; 30:30-34 ("Since the concentration of bendamustine is higher in a 30% TBA/water saturated solution as compared with other alcohol solutions, it is anticipated that the vial size required to fill 100 mg of bendamustine can be decreased from the current Ribomustin® presentation."); 30:47-48 ("Mannitol was selected as the bulking agent in order to maintain a formulation similar to Ribomustin®."); 31:31-35 ("Based on our experience with several lyophilization solvent systems and not wishing to be bound

to any particular theory, the problems associated with Ribomustin® reconstitution may be associated with precipitation caused by melt back during lyophilization."); 31:40-43 ("Lyophilates produced with 30% (v/v) TBA according to the invention reconstitute within 3-10 minutes as compare to commercially available Ribomustin which may take 30-45 minutes."); 31:58-62 ("Major impurities introduced during Ribomustin® manufacturing, compounding, fill, and lyophilization procedure, as determined by HPLC analysis (FIG. 6), are the hydrolysis product HP1, the Dimer, and the ethyl ester of bendamustine, BM1EE.").

Despite these extensive disclosures, the Examiner nonetheless allowed the claims over references detailing RIBOMUSTIN®. The Rote Liste adds nothing to these disclosures that was not already considered during prosecution.

Similarly, the teachings relied upon by Agila concerning TBA were also disclosed in the specification. At Column 2, lines 60-62 of the '190 Patent, for example, it states "Teagarden *et al.* disclose[s] lyophilized formulations of prostaglandin E-1 made by dissolving PGE-1 in a solution of lactose and tertiary butyl alcohol (U.S. Pat. No. 5,770,230)," Ex. 1001. U.S. Patent No. 5,770,230 to Teagarden *et al.* (Ex. 2011) discloses essentially the same teachings regarding TBA relied upon by Agila as the Teagarden article (Ex. 1007). Despite this disclosure, the Examiner nonetheless allowed the claims.

The Board should not waste its resources revisiting these issues that are so similar to those already reviewed by the Examiner. But if the Board is inclined to consider the Rote Liste and Teagarden – despite the Examiner's previous consideration of very similar teachings – the combination does not render obvious the claims of the '190 Patent.

b. The Combination of the Rote Liste and Teagarden Is Only Arrived at Through Hindsight Reasoning

Agila's obviousness arguments collapse the obviousness analysis into nothing more than a hindsight-guided combination of elements. The record, however, discloses several reasons why a person of ordinary skill in the art would not have been motivated to try, let alone make, the claimed invention of the '190 Patent.

The '190 Patent's specification discloses that bendamustine compositions like RIBOMUSTIN® were marketed in Germany for more than ***forty years*** prior to the invention. (Ex. 1001 at 1:50-57.) After all that time, it was the inventors of the '190 Patent who set out to determine if it was possible to create a lyophilized formulation of bendamustine that is "easier to reconstitute" and has "a better impurity profile" than products such as RIBOMUSTIN®. (*Id.* at 2:29-32.)

Following lengthy testing, the inventors created a composition of bendamustine (or bendamustine hydrochloride), mannitol, TBA and water they

found, among other things, unexpectedly stabilized the formulation such that bendamustine degradation was negligible. This significant improvement over the prior art formulations of bendamustine and mannitol (like RIBOMUSTIN®) was recognized by the Examiner in his reasons for allowance of the challenged claims. (Ex. 1005 at Notice of Allowability dated August 29, 2012 at 3.)

The '190 Patent was not simply a combination of elements found in the prior art, but was an invention that resulted from a recognition of a manufacturing, stability, storage, and reconstitution problem that was associated with bendamustine. Indeed, not one of the many references cited by Agila – except the '190 Patent itself – identified any problem with existing bendamustine/mannitol compositions or described prior attempts to solve it. (Petition at 22, citing '190 Patent as disclosing the problem to be solved.) That the references put forth by Agila could be combined to solve this problem (recognized only by the inventors) is only straightforward in hindsight. Agila points to no evidence that anyone sought to improve bendamustine compositions using, *e.g.*, TBA, in the many decades they had been available. ***Indeed, Agila cannot even cite to a single reference that suggests "improving" bendamustine/mannitol compositions at all, much less with TBA***. Even after RIBOMUSTIN® became available in 1995, and the Rote Liste in 1996, no one sought to improve it by adding TBA until nearly 10 years later when the inventors achieved their success.

Nor can the evidence put forth by Agila support a finding that TBA would have been expected to solve any problems associated with bendamustine had they been identified. Teagarden itself reminds potential formulators that "[o]ne should remember that successful sterile formulations should always employ ***an understanding of the fundamental interrelationships between the formulation, the process, and the package***. The knowledge gained from the interrelationships enables optimization of the formulation which can be processed and packaged at a production scale," Ex. 1007 at 116 (emphasis added). These "same principles still apply to the use of organic solvents in freeze-drying. The advantages and disadvantages of their use must be carefully weighed before they are chosen to be used in the manufacture of a pharmaceutical product, ***especially one that is an injectable dosage form***." (*Id.* (emphasis added); *see also id.* at 131 ("the practicalities of use of these co-solvent systems must be properly assessed ***before they should be considered for use***. This especially applies when using them in the manufacturing of a pharmaceutical product," emphasis added.).) Nevertheless, according to Agila, Teagarden would prompt a formulator to reasonably expect that bendamustine, mannitol, and TBA would exhibit improved stability and solubility. But with results dependent on the particular formulation, process, and package at issue, an ordinary artisan would not have been motivated to pluck TBA from the many co-solvents of Teagarden and combine it with the composition

disclosed in the Rote Liste, particularly since Teagarden makes no disclosure whatsoever concerning bendamustine or related compounds. Agila's grounds must be denied on that basis alone.

Agila's allegation that one of ordinary skill would have been capable of selecting the correct formulation from various available alternatives in Teagarden is also unfounded. Based on the breadth of choices and numerous combinations, the prior art would not have rendered the invention obvious to try. In fact, testing by the inventors led to the unexpected discovery that lyophilates produced with 30% (v/v) TBA according to the invention reconstituted within 3-10 minutes as compared to RIBOMUSTIN®, which may take 30-45 minutes. (Ex. 1001 at 31:40-43.) Agila fails to sufficiently show that a skilled formulator would have reasonably predicted this innovation when choosing from the several co-solvent systems disclosed in Teagarden. Rather, the possible approaches to solving the bendamustine problem were not known or finite, and the solution was not predictable. As such it would not have been obvious for a person or ordinary skill in the art to make the claimed invention.

Teagarden's guidance concerning co-solvent systems also highlighted the unpredictability of the proposed combination. Teagarden cautioned the development scientist to be aware that use of "***these organic/water co-solvent***

systems can cause a multitude of problems." (Ex. 1007 at 116, emphasis added.)

For example:

> toxicity concerns, operator safety concerns due to high degree of flammability or explosion potential, lack of compendia grades or monographs, may require special manufacturing facilities/equipment or storage areas, possess difficult handling properties, requires high purity solvent with known impurities at low levels, must reach acceptable residual solvent in final product, high cost to use, potential for splash/spattering of product in vial neck, and lack of regulatory familiarity.

(*Id.* at 116.) According to Teagarden, "the potential disadvantages and issues which must be evaluated include: the proper safe handling and storage of flammable and/or explosive solvents, the special facilities or equipment which may be required, the control of residual solvent levels, the toxicity of the remaining solvent, quantification of an appropriate GMP purity, the overall cost benefit to use of the solvent, and the potential increased regulatory scrutiny," *id.* at Abstract. Teagarden further warns that "use of co-solvents can sometimes have deleterious effects during freezing. The use of volatile organic solvents has been reported to result in drug precipitation in the latter parts of freezing due to solvent evaporation. This can lead to an increase in drug concentration above its saturation level (Seager, 1979b)." *Id.* at 119.

Regarding *tert*-butanol in particular, Teagarden contains numerous warnings. One should be aware, Teagarden says, "of the potential for a reflux type phenomenon when using highly volatile solvents such as *tert*-butanol. This situation can happen when the evaporating *tert*-butanol condenses near the top of the vial and forms a stream of solvent returning to the solution." (*Id.* at 119.) After freeze-drying has been completed, the vial can contain spots of powder near the neck of the vial. The presence of dried powder near the neck of a vial, according to Teagarden, "is not desired because of both a poor appearance and the possibility of negatively impacting the seal with the rubber closure," (*id.*). Most importantly, Teagarden cautions that "when using [a *tert*-butanol] solvent system [with injectable pharmaceuticals], ***both formulation and process control required optimization*** to maximize drying rates and to minimize residual solvent levels at the end of drying," (*Id.* at Abstract, emphasis added.)

Any of these "***multitude of problems***" with the use of co-solvents in general, and *tert*-butanol in particular, as disclosed by Teagarden would discourage any formulator from using TBA because of the unpredictability of the results, especially with an injectable pharmaceutical like existing compositions of bendamustine and mannitol.

Observations made after the invention of the '190 Patent by others that bendamustine/mannitol compositions are especially difficult to formulate and

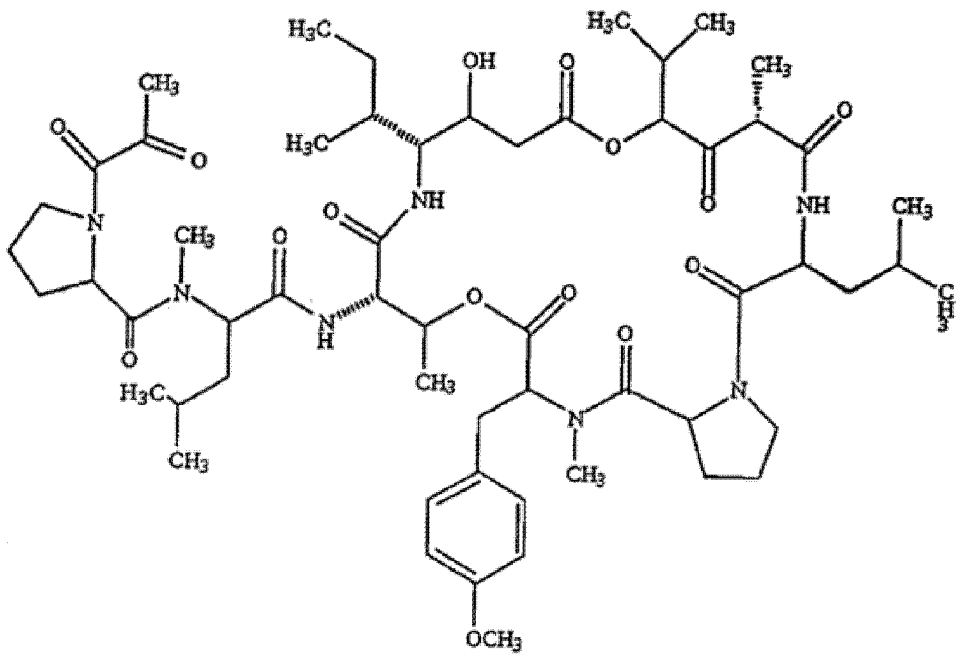
manufacture underscore its nonobviousness. Such observations were even made by competitors of Cephalon. For example, another patent application points out that "reconstitution of the lyophilized powder is difficult and the reconstitution time depends on the solvent used during lyophilisation and the manufacturing parameters" and "nitrogen mustards are difficult to formulate as pharmaceuticals." (Ex. 2013, U.S. Patent Publication No. 2014/0142153 at ¶¶ 0006 and 0016.) In fact, they recognize that "[t]o lower the rate of degradation of bendamustine HCl, solvent systems for manufacturing bulk solution, the sequence of addition of ingredients, temperatures, duration of critical steps in lyophilization, and the like can be critical." (*Id.* at ¶ 0017, emphasis added.)

c. Nuijen and Gust are Inapposite

The references Agila uses in support of its Grounds 2 and 3 are inapposite. Only with improper hindsight can Agila depict them as even relevant. *See Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to guard against slipping into the use of hindsight); *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1138 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

Nuijen is a 2000 publication that describes the development of a lyophilized dosage form of aplidine. (Ex. 1008.) Aplidine is "a novel representative of an

evolving group of anticancer agents derived from marine sources." (*Id.* at 193.) Aplidine, dehydrodidemnin B (*see* structure in Figure below) is a marine depsipeptide isolated from *Aplidium albicans* that shows strong antitumor activity. (Broggin, et al., "Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4," *Nature*, September 2002, Ex. 2012.)



(*Id.*) Agila claims that one of ordinary skill in the art would have been motivated by Nuijen to formulate an anti-cancer drug with *tert*-butanol, in an attempt to remedy the glaring deficiency in Teagarden that the drugs disclosed ***are entirely unrelated to bendamustine***. But Agila's reliance is misplaced. Bendamustine and aplidine are significantly distinct from each other, both structurally and physico-

chemically. Agila provides no evidence whatsoever that demonstrates any similarities between the two. It is well known to those skilled in the art that the physical-chemical properties of a compound greatly affect the successful formulation of the compound. Nevertheless, Agila claims that aplidine and bendamustine are both antiproliferative active agents and alleges, therefore, that since aplidine and bendamustine are in the same drug class, that methods of lyophilizing aplidine could be extended to the lyophilization of bendamustine. This reasoning cannot support a finding of obviousness, though, because Agila has failed to demonstrate that the suggested combination of references would predictably produce the claimed invention. That aplidine and bendamustine are in the same broad therapeutic class, *i.e.*, antiproliferative agents, is irrelevant. Formulation, in particular, lyophilization, depends solely on the physical-chemical properties of the chemical compounds and has nothing whatever to do with the disease state to be treated with the compound. Agila has not demonstrated that methods of stabilizing aplidine would predictably stabilize the chemically dissimilar bendamustine or its hydrochloride salt. Merely identifying that both compounds are antiproliferative agents is insufficient evidence to establish obviousness. And Nuijen provides no motivation for further development of anything beyond aplidine. Nuijen thus does not resolve the deficiencies of the Rote Liste in view of Teagarden.

Likewise, Gust fails to provide the motivation articulated by Agila. Gust is a 1997 publication that describes a high performance liquid chromatography analysis ("HPLC") of RIBOMUSTIN®. Gust discloses nothing about how to improve RIBOMUSTIN®, or even that improvement is needed. As a result, Agila must resort to manufacturing a motivation to combine the references with Gust by pointing ***to the '190 Patent itself***. (Petition at 50.) This, however, is the height of hindsight reasoning and must be rejected.

None of the cited art would motivate a person of ordinary skill in the art to change the RIBOMUSTIN® formulation used successfully for more than forty years, or to reasonably expect that a solution comprising mannitol, TBA, and water could be used to improve its reconstitution and stability properties as shown in the '190 Patent. And given that Agila's obviousness arguments regarding Grounds 2 and 3 rest on supposed motivation from Nuijen and/or Gust, those arguments cannot survive. *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 at 1357 (Fed. Cir. 2007) ("It remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.").

d. Unexpected Results and Objective Indicia Show The '190 Patent's Inventiveness

In addition to being nonobvious in view of the Rote Liste, Teagarden, Nuijen, and Gust, both unexpected results and other objective facts underscore the '190 Patent's inventiveness.

Objective indicia are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness." *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008); *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) ("Whether before the Board or a court, this court has emphasized that consideration of the objective indicia *is part of* the whole obviousness analysis, not just an after-thought.") (internal citations omitted). "Thus, the Board should give the objective indicia its proper weight and place in the obviousness analysis, and not treat objective indicia of nonobviousness as an afterthought." *Id.* at 1358. Doing so allows the Board "to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, objective indicia alone can defeat an invalidity challenge even if the patent is otherwise *prima facie* obvious.

In IPR2013-00265, for example, the Board rejected an IPR petition that had established *prima facie* obviousness based solely on objective indicia. *See Omron*

Oilfield & Marine, Inc. v. MD/Totco, IPR2013-00265, 2013 WL 8595961 at *10 (Patent Tr. & App. Bd. October 31, 2013) ("Evidence of secondary considerations, taken as a whole, supports our decision that the Petitioner has not demonstrated a reasonable likelihood that the invention . . . is obvious.").

The objective indicia here are substantial, including unexpected results; regulatory approvals; acclaim of others; commercial success; and copying by others. Agila addresses none of these indicia:

- **Regulatory Approvals**: Regulatory approval can confirm a patent's inventiveness. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (regulatory approval relevant in evaluating the objective indicia of nonobviousness). The FDA approved TREANDA® for two indications and also granted TREANDA® orphan drug status for both indications. (Ex. 2001.) That regulators noticed the innovation reflected in the patent adds substantial weight to the conclusion that the patent reflects a novel invention.
- **Acclaim of Others**: TREANDA® has received substantial acclaim from industry groups, doctors and the market itself. (Ex. 2002.) This factor also weighs heavily in favor of the '190 Patent's inventiveness. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("indicators of industry acclaim" are relevant to inventiveness).

- **Commercial Success**: "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). TREANDA® has been a huge commercial success. *In re McLaughlin*, 443 F.2d 1392, 1396 (C.C.P.A. 1971) (commercial success shown by high volume of first-year sales coupled with articles praising the invention). There is ample evidence of commercial success here, and the required "nexus" of that success to the '190 Patent's invention. *Id.*; *see also, e.g., Syntex (U.S.A.) LLC v. Apotex Inc.*, 2006 WL 1530101, at *26 (N.D. Cal. June 2, 2006) (finding that "commercial success derives from its embodiment of the entire combination taught by the '493 patent, and not from the fact that its active ingredient . . . was previously protected by another patent"). TREANDA® sales in the United States exceeded $3 billion dollars. (Ex. 2005-2010.)
- **Unexpected Results**. "Unpredictable and unusual properties" weigh in favor of inventiveness. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008). Unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted." *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (internal

quotation marks omitted). Unexpected results are further objective evidence that an invention represents an advance in the art. For the several reasons discussed above, the inventors discovered that adding TBA to the bendamustine/mannitol composition produced a variety of unexpected and desirable results. For example, the inventors discovered that the effect of alcohols, particularly TBA, 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 the bendamustine. (Ex. 1001 at 30:9-22; Figs. 2-4.) During prosecution, the Examiner acknowledged these unexpected results. Ex. 1005 at Notice of Allowability dated February 4, 2013 at 2 ("Applicant has unexpectedly found that the addition of tertiary-butyl alcohol stabilizes the formulation such that bendamustine degradation is negligible (no more than 0.5% formation of bendamustine ethyl ester")).

- **Copying by Others**: "Copying is an indicium of nonobviousness, and is to be given proper weight" in analyzing the objective indicia of inventiveness. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988). Here, others – including Agila and Mylan – have tried to copy Cephalon's invention, as described in Cephalon's complaints against them. *See, e.g.*, Ex. 1012.

B. Ground 4: The Rote Liste Does Not Anticipate Claims 4, 5, 7, and 8

Anticipation focuses on whether the prior art makes the "claimed combination…immediately apparent." *W.M. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012). "For a prior art reference to anticipate a claim, it must disclose all of the limitations of the claim, 'arranged or combined ***in the same way as in the claim***.'" *Id.* at 1361-63 (emphasis added). The patent's particular claim language is thus central to assessing anticipation. *Sanofi*, 550 F.3d at 1082 (anticipation "requires that ***every element and limitation of the claim*** was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention," (emphasis added)).

Here, the patent's claim of a composition including TBA and water is indisputably nowhere disclosed in the Rote Liste. The Rote Liste merely discusses a dry composition of bendamustine and mannitol.

To portray the Rote Liste as anticipatory, Agila must adopt a claim construction that reads out claims 4, 5, 7, and 8's dependency on claim 1. Agila does so by asserting that these dependent claims are "product-by-process" claims, a facially unreasonable construction that would read out the explicit recitation of pharmaceutical compositions made from ***the composition of claim 1***. But claim 1

does not recite a process. It recites a composition. This kind of re-writing of the claims was previously rejected by the Federal Circuit in *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356, 1362 (Fed. Cir. 2005). In *Norian*, the court accepted that a solution could be defined by "the ingredients used to make the solution." *Norian*, 432 F.3d at 1362. The court found that the characterization of a "solution in terms of the components put into it" was a "conventional means of describing a solution." *Id.* The court concluded that defining the solution of the asserted claims in terms of the ingredients used to make the solution did not convert the claims into product-by-process claims, but rather the claims remained product claims "limited to the designated ingredients from which the claimed solution was made." *Id.*

Here, the Board is confronted with a situation similar to that in *Norian*. In drafting its claims, Cephalon was allowed to describe the pharmaceutical composition of claims 4, 5, 7, and 8 in terms of its parts – the composition of claim 1. Claim 1 is not a ***process*** claim, it is a ***composition*** claim. That claim 1 requires a composition having TBA and water cannot be disregarded. Therefore, the Board should reject Agila's construction that impermissibly attempts to rewrite the dependent product claims as product-by-process claims.

Even if the Board adopts Agila's proposed construction and views claim 4 as a product-by-process claim, Agila still has not met its burden of showing that the Rote Liste discloses the lyophilized pharmaceutical composition of claim 4. Claim

4 requires that the lyophilized pharmaceutical composition be made from the composition of claim 1, which recites bendamustine hydrocholoride, mannitol, TBA, and water. Agila alleges that the Rote Liste teaches a lyophilized pharmaceutical composition made from bendamustine, mannitol, ***ethanol***, and water.[3] (Petition at 26, emphasis added.) Agila fails to provide any evidence, however, that the features of a lyophilized composition made using ethanol are the same as a lyophilized pharmaceutical composition made using TBA. In fact, the record evidence shows that the features of these lyophilized compositions are demonstrably different from one another. The specification of the '190 Patent describes in detail how a lyophilized pharmaceutical composition made from bendamustine hydrocholoride, mannitol, TBA, and water differs from one made from a composition of bendamustine, mannitol, ethanol, and water. *See, e.g.*, Ex. 1001 at Col. 31:39-42 ("Lyophilates 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."); 31:6-10 ("The lyophilized vials filled from solutions of 10% ethanol, 20% ethanol…produced either a collapsed cake or a film residue. The…solvent system producing an acceptable cake was 30% TBA.") Agila has produced no evidence to the contrary. The Rote Liste thus cannot anticipate and Agila's Ground 4 must be rejected.

[3] This is nowhere disclosed in the Rote Liste itself.

V. AGILA'S PETITION VIOLATES THE BOARD'S RULES

The Petition is also fatally defective on procedural grounds. Agila's proposed grounds are redundant, which is prohibited. *See Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2012-00003, 2012 WL 9494791, at *2 (Patent Tr. & App. Bd., October 25, 2012). The Rote Liste is alleged to be both anticipatory and an obviousness reference. Thus, either the anticipation ground or the obviousness ground is redundant. The Rote Liste is also used as a primary reference in combination with Teagarden, Teagarden plus Nuijen, and Teagarden plus Nuijen and Gust. This creates several redundant, parallel grounds of rejection.

To avoid dismissal of a proposed ground of unpatentability, a petitioner must "provide a meaningful distinction between the different, redundant rejections." *Illumina, Inc. v. Tr. of Columbia Univ.*, IPR2012-00006, 2013 WL 5653110 at *7 (Patent Tr. & App. Bd., May 10, 2013) (*citing* 37 C.F.R § 42.1(b)). Where multiple references have been cited for the same facts, it is not enough for a petitioner to argue that the cited references are not identical, or to "speculate[] that in certain publications an element may be more clearly set forth in one publication rather than another." (*Id.*) Rather, a petitioner must explain the differences between the references and "how this difference would impact the unpatentability challenge." (*Id.*) Here, Agila did not set forth a sufficient explanation or rationale.

Accordingly, the petition should be denied, or in the alternative, the redundant grounds should be denied.

VI. CONCLUSION

For all of the foregoing reasons, the Board should decline to institute an *inter partes* review on any of the Petition's proposed grounds.

Respectfully submitted,

/Eleanor M. Yost/

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Dated: April 21, 2015

PATENT OWNER'S LIST OF EXHIBITS

Exhibit	Description
2001	TREANDA® Prescribing Information
2002	M. Tirrell, "Cephalon's Treanda Poised for 10-Fold Sales Surge (Update3)," *Bloomberg*, December 7, 2009
2003	"How did TREANDA do in Clinical Trials?" http://www.treanda.com/cll/about-treanda/treanda-clinical-trials.aspx
2004	"FDA approves bendamustine hydrochloride for NHL," *Healio HemOnc Today*, Nov. 4, 2008
2005	J. George, "Cephalon drug Treanda passes $1B in sales," *Philadelphia Business Journal,* July 8, 2011
2006	Cephalon, Inc. 10-K, 2008
2007	Cephalon, Inc. 10-K, 2009
2008	Cephalon, Inc. 10-K, 2010
2009	Teva Pharmaceutical Industries Limited 20-F, 2011
2010	Teva Pharmaceutical Industries Limited 20-F, 2014
2011	U.S. Patent No. 5,770,230 (Teagarden)
2012	M. Broggin, et al., "Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4," *Nature*, September 17, 2002
2013	U.S. Patent Publication No. 2014/0142153 (Kocherlakota)

CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **CEPHALON, INC.'S PRELIMINARY PATENT OWNER RESPONSE** and the exhibits cited therein were served electronically via e-mail on April 21, 2015 on the following:

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Counsel for Patent Owner

Dated: April 21, 2015