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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

J KYLE BASS and ERICH SPANGENBERG,
Petitioner,

v.

FRESENIUS KABI USA, LLC,
Patent Owner.

Case IPR2016-00254
Patent 8,476,010 B2

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

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

J Kyle Bass and Erich Spangenberg (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 13–15, 17, 18, 20, and 24–28 of U.S. Patent No. 8,476,010 B2 (Ex. 1001, "the '010 patent"). Paper 1 ("Pet."). Fresenius Kabi USA, LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp.").

On June 8, 2016, we instituted an *inter partes* review of claims 1, 13–15, 17, 18, 20, and 24–28 of the '010 patent on two grounds of obviousness. Paper 9 ("Dec. Inst."), 19. Patent Owner filed a Response to the Petition. Paper 28 ("PO Resp."). Petitioner filed a Reply to Patent Owner's Response. Paper 31 ("Pet. Reply").

Patent Owner filed observations on the cross-examination of Petitioner's declarant, Thomas N. Feinberg, Ph.D. Paper 36. Petitioner filed a response to Patent Owner's observations. Paper 40.

An oral hearing was held on March 13, 2016, a transcript of which has been entered in the record. Paper 46 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1, 13–15, 17, 18, 20, and 24–28 of the '010 patent are unpatentable.

A. Related Proceedings

The parties identify several district court proceedings as relating to the '010 patent. Pet. 3; Paper 5, 1–2. None of the proceedings is currently pending, and Petitioner is not a party to any of the proceedings. Pet. 5.

Patent Owner also identifies Case No. IPR2015-00715, where a different Petitioner also challenged the ’010 patent. Paper 5, 2. That proceeding was terminated before institution. *Dr. Reddy’s Labs., Inc. v. Fresenius Kabi USA, LLC*, Case IPR2015-00715, Paper 12 (PTAB Apr. 2, 2015).

B. The ’010 Patent

Propofol (2,6-diisopropylphenol) is a well-known intravenous anesthetic agent. Ex. 1001, 1:14–15. The ’010 patent relates to pharmaceutical formulations of propofol that are stored in containers having nonreactive, inert closures. *Id.* at 1:8–10. Propofol is a hydrophobic, water-insoluble oil that must be incorporated with solubilizing agents, surfactants, or an oil-in-water emulsion. *Id.* at 1:20–23.

Propofol compositions have been the subject of several patents. *Id.* at 1:26–27. The formulation described in U.S. Patent No. 5,714,520 is sold as Diprivan, which comprises “a sterile, pyrogen-free emulsion containing 1% (W/v) propofol in 10% (w/v) soybean oil.” *Id.* at 2:33–36. According to the Specification, the inventors recognized that the relatively high volume of soybean oil used in prior art formulations protects propofol from degradation in a container. *Id.* at 3:63–66. Thus, the Specification states that “at oil contents (and/or propofol solvent contents) lower than about 10% (w/v), degradation of propofol has been found to occur if the container closure is not inert or non-reactive to propofol.” *Id.* at 3:66–4:2. Preferred closures include those “coated or treated with inert materials such as siliconized polymer.” *Id.* at 9:43–45.

C. Illustrative Claim

Petitioner challenges claims 1, 13–15, 17, 18, 20, and 24–28 of the ’010 patent, of which claim 1 is the only independent claim. Claim 1 is illustrative and is reproduced below:

> 1. A sterile pharmaceutical composition of propofol in a container, comprising:
>
> a container which includes a closure and a composition in the container, and
>
> the composition in the container comprising from 0.5% to 10% by weight propofol and from about 0 to about 10% by weight solvent for propofol,
>
> where when the composition in the container sealed with the closure is agitated at a frequency of 300–400 cycles/minute for 16 hours at room temperature, the composition maintains a propofol concentration (w/v) measured by HPLC that is at least 93% of the starting concentration (w/v) of the propofol;
>
> where the closure is selected from the group consisting of siliconized bromobutyl rubber, metal, and siliconized chlorobutyl rubber.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial on the following grounds:

Reference	Basis	Claims challenged
Diprivan PDR[1] in view of Farinotti[2] and van den Heuvel[3]	§ 103	1, 13–15, 17, 18, 20, and 24–28
Diprivan PDR in view of Farinotti and Lundgren[4]	§ 103	1, 13–15, 17, 18, 20, and 24–28

II. ANALYSIS

A. The Level of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art would have been someone with substantial research or industry experience in pharmaceutical drug product development, including experience with sterile drugs and their packaging, and having at least a master's degree or doctorate in a related technical field, such as analytical, physical or organic chemistry, chemical engineering, pharmaceutics or related subject matter or having equivalent experience in such fields. Pet. 8. In its Preliminary Response, Patent Owner largely agreed with Petitioner's definition, with the exception that Patent Owner's definition requires experience with propofol and drug product emulsions, emulsion systems and their packaging. Prelim. Resp. 19.

In our Decision to Institute, we adopted Patent Owner's definition, given the claims recite compositions of propofol in a container. Dec. Inst. 5.

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[1] Physicians' Desk Reference, Product Identification Guide and Product Information for Diprivan, 341, 2939–45 (1997) ("Diprivan PDR," Ex. 1005).
[2] R. Farinotti, *Interactions physicochimiques et mode de conservation du Diprivan* ® [Physio-Chemical Interactions and Storage of Diprivan®], 13 Ann. Fr. Anesth. Reanim. 453–56 (1994) (Ex. 1006). Citations to Farinotti in this Decision are to the certified translation provided as Ex. 1007.
[3] J.G. van den Heuvel, US 5,383,864, issued Jan. 24, 1995 (Ex. 1010).
[4] Lundren et al., WO 00/12043, published Mar. 9, 2000 (Ex. 1031).

Patent Owner notes that Petitioner's declarant, Dr. Feinberg, agreed that this addition to the definition was appropriate. PO Resp. 5 (citing Ex. 2035, 203:11–15). Based on the complete trial record, we see no reason to deviate from our prior definition of a person of ordinary skill in the art. That is, we adopt the level of ordinary skill set forth by Patent Owner. Moreover, we note that the prior art itself further demonstrates the level of skill in the art at the time of the invention. *Cf. Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

Patent Owner challenges the expertise of Petitioner's declarant, Dr. Feinberg. PO Resp. 6–7. In particular, Patent Owner asserts that because Dr. Feinberg lacks expertise in emulsion formulations, manufacturing, and propofol, his opinions should be given limited weight. *Id.* Petitioner, on the other hand, challenges the credibility of Dr. Davis, asserting that Dr. Davis has no experience in filling and packaging pharmaceutical products. Pet. Reply 1 (citing Ex. 1043, 38:9–12).

The record shows Dr. Feinberg has some experience with emulsion drug products (Ex. 2035, 16:15–21), with the use of siliconization to improve manufacturing efficiency with drug products (*id.* at 26:6–27:20), and possibly with propofol, although Dr. Feinberg could not recall (*id.* at 23:8–24:23). Dr. Davis admits he does not have experience in filling and packaging of pharmaceutical products, but testifies that a person of ordinary skill in the art, as necessary, would consult someone with such experience. Ex. 1043, 37:15–38:12.

We find a person of ordinary skill in the art would have had experience with propofol and drug product emulsions, emulsion systems, and their packaging. Dr. Feinberg has less experience than Dr. Davis with propofol and emulsions, whereas Dr. Davis has less experience than Dr. Feinberg with pharmaceutical packaging. Given their relative experiences, we decline to discount the opinion of either declarant based solely on their differing areas of expertise.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we give 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 re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

The parties do not contest the constructions of the following terms:

Term	**Proposed Construction**
"from about 0 to about 10% by weight solvent for propofol"	"from approximately zero to approximately 10% solvent by weight, a range that includes 10%"
"siliconized"	"surface-treated, coated, or manufactured with silicone or one or more siloxane polymers"
"inert to propofol"	"having no significant reactivity to propofol"

Pet. 8–12; PO Resp. 5. Based on the record before us, we construe these terms as noted above.

Moreover, having considered the complete trial record, we determine that it is unnecessary to expressly construe any additional claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention

does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). A "reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.*

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

D. Obviousness over Diprivan PDR, Farinotti, and van den Heuvel

Petitioner asserts that claims 1, 13–15, 17, 18, 20, and 24–28 are unpatentable as obvious over Diprivan PDR, Farinotti, and van den Heuvel. Pet. 22–34. Patent Owner opposes Petitioner's assertion. PO Resp. 23–51. Based on the full trial record, we determine that Petitioner has established by a preponderance of the evidence that claims 1, 13–15, 17, 18, 20, and 24–28 are unpatentable over the cited art.

1. Diprivan PDR (Ex. 1005)

Diprivan PDR provides product information regarding Diprivan. Diprivan PDR states propofol is very slightly soluble in water and is formulated in a white, oil-in-water emulsion. Ex. 1005, 2939. Diprivan contains 10 mg/ml of propofol and 100 mg/ml of soybean oil (*id.*) in either a 50 or 100 mL infusion vial with a rubber stopper (*id.* at 2945).

2. Farinotti (Ex. 1007)

Farinotti describes the physiochemical interactions and stability of Diprivan. Farinotti explains that propofol is a phenol, which may oxidize in the presence of oxygen into two degradation products. Ex. 1007, 453. Farinotti states that "[s]torage in diverse conditions (ampoules, vials) at an ambient temperature (25ºC) for three years did not show any changes in the characteristics of the drug." *Id.* at 454. Farinotti further states that in glass vial packaging, Diprivan has good stability and "a lack of adsorption of propofol on the bromobutyl stopper." *Id.*

3. van den Heuvel (Ex. 1010)

van den Heuvel relates to a pre-filled injection device with a liquid diazepam formulation. Ex. 1010, 1:8–11. van den Heuvel states that it is an object of the invention to provide a device where the diazepam formulation "can be stored in prolonged contact with at least one rubber sealing member without unacceptable deterioration in quality of said formulation taking place." *Id.* at 2:40–46. van den Heuvel further states that bromobutyl rubber, in contrast with chlorobutyl rubber, does not cause unacceptable deterioration in quality after prolonged contact with the diazepam formulation. *Id.* at 2:62–66. van den Heuvel discloses the results of storage stability testing of liquid diazepam formulations using different rubber stoppers. *Id.* at 4:53–5:39. The rubber stoppers and glass barrels are pre-treated "in the conventional manner by washing, siliconising and sterilising." *Id.* at 4:61–64. The barrels are stored at a given temperature for a given period of time and then the diazepam concentration is determined by high performance liquid chromatography ("HPLC"). *Id.* at 5:1–4.

4. Analysis

Regarding claim 1, Petitioner asserts that Diprivan PDR in view of Farinotti teaches each limitation of claim 1 except the use of a "siliconized" bromobutyl rubber stopper. Pet. 23–25. Having reviewed the arguments and evidence, we agree with Petitioner and note that Patent Owner does not dispute Petitioner's argument. For example, Diprivan PDR discloses a composition in a vial with a rubber stopper with 1% propofol by weight/volume, which is within the 0.5% to 10% range claimed. Ex. 1005, 2939, 2945; Ex. 1002 ¶ 13. Although Diprivan PDR does not specify the type of rubber used for the closure, Farinotti teaches that the closures used in Diprivan were bromobutyl rubber stoppers. Ex. 1007, 454. Diprivan PDR also states that Diprivan contains 10% soybean oil, which is within the claimed range of "from about 0% to about 10%" for the solvent. Ex. 1005, 2939; Ex. 1002 ¶ 13.

Regarding the "stability limitation,"[5] we agree with Petitioner that this limitation is an inherent property of Diprivan that the patentee of the '010 patent has observed and confirmed through testing. Pet. 23–24; Ex. 1002 ¶¶ 15–16. For instance, Example 34 of the '010 patent discloses the testing of various propofol compositions with rubber closures, including Diprivan, for propofol degradation or potency. Ex. 1001, 25:10–45; *see also id.* at 23:21–23. The testing method involves agitating vials of propofol at a

[5] For ease of reference, we refer to the limitation "where when the composition in the container sealed with the closure is agitated at a frequency of 300–400 cycles/minute for 16 hours at room temperature, the composition maintains a propofol concentration (w/v) measured by HPLC that is at least 93% of the starting concentration (w/v) of the propofol" as "the stability limitation."

frequency of 300–400 cycles/minute at room temperature for 16 hours and comparing HPLC assay results of the samples before and after testing to determine if there is a loss in potency or concentration of propofol in the formulations, as required by claim 1. *Id.* at 23:29–34. Example 34 discloses that 99.3% of the propofol in Diprivan remained after the stability testing. *Id.* at 25:31. That result is consistent with the Specification's statement that prior art formulations containing 10% soybean oil, like Diprivan, are protected from propofol degradation. *See id.* at 27:4–7, 3:63–66; Ex. 1002 ¶ 15.

Regarding the "siliconized" bromobutyl rubber stopper limitation, van den Heuvel discloses the use of siliconized bromobutyl rubber stoppers with a liquid diazepam formulation. Ex. 1010, 4:56–5:1, 5:8–32 (Table A and Table B). Petitioner asserts that a person of ordinary skill in the art would have had a reason to substitute a siliconized bromobutyl rubber stopper of van den Heuvel for the bromobutyl rubber stopper of Diprivan because van den Heuvel states a desire to develop a pharmaceutical composition that can be stored in prolonged contact with at least one rubber sealing member "without unacceptable deterioration in quality." Pet. 26 (citing Ex. 1010, 2:43–46). Dr. Feinberg explains that the siliconized bromobutyl rubber closures fulfilled that desire by providing an inert sealing member that did not react with the pharmaceutical composition. Ex. 1002 ¶ 18. Petitioner further asserts that the known advantages of using siliconized rubber closures, such as improved machinability, processing efficiencies, and ease of insertion or lubricity, would have further motivated an ordinary artisan to use a siliconized bromobutyl rubber stopper with a reasonable expectation of success. Pet. 26–27 (citing Ex. 1002 ¶¶ 20, 21, 23; Ex. 1004, S4).

a. Reason to Combine

After reviewing the arguments and evidence, we are persuaded that a person of ordinary skill in the art would have had a reason to use a siliconized bromobutyl rubber stopper with the claimed propofol formulation. Consistent with our Institution Decision, we remain unpersuaded by Petitioner's argument that an ordinary artisan reading van den Heuvel would have concluded that it was the siliconization of the bromobutyl rubber stoppers that imparts a stable solution of diazepam. *See* Pet. 26 (citing Ex. 1010, col. 5, Table A and Table B). Indeed, Petitioner's declarant, Dr. Feinberg, testified that he agrees with our determination. Ex. 2035, 208:24–209:4. van den Heuvel concludes that "chlorobutyl stoppers cause a considerably larger decrease of the diazepam content than the stoppers manufactured from . . . bromobutyl rubber." Ex. 1010, 5:34–37. But because both the chlorobutyl stoppers and the bromobutyl stoppers were siliconized, and van den Heuvel does not compare the use of siliconized stoppers to unsiliconized stoppers, the results of Tables A and B suggest nothing about the effect of siliconizing stoppers on the stability of the formulation. *See* Ex. 2036 ¶ 84.

Nevertheless, having considered the full trial record, we are persuaded that a person of ordinary skill in the art would have recognized the advantages of siliconizing rubber closures, such as ease or efficiency during manufacture, and would have had a reason to siliconize the bromobutyl rubber closure of Diprivan with a reasonable expectation of success. *See* Ex. 1002 ¶¶ 20–24; Ex. 1004, S4. Dr. Feinberg testifies in his declaration that "[u]ncoated stoppers . . . while having good properties including low propofol reactivity with 10% soybean oil formulations and low cost, had known issues with regard to machinability." Ex. 1002 ¶ 20. The "known

issues" include sticking to each other and to the filling line assemblies that would necessitate frequent line maintenance or low line speed. *Id.*; Ex. 1044 ¶¶ 6–7 (citing Ex. 1004, S4; Ex. 1045, 361).

Patent Owner argues that any purported manufacturing benefits of siliconization would not have motivated a person of ordinary skill in the art to replace the commercially successful Diprivan rubber stoppers because Petitioner does not offer any evidence that Diprivan stoppers experienced any sticking problems or other manufacturing issues. PO Resp. 28–29. Patent Owner notes that Petitioner's declarant, Dr. Feinberg admitted that he was not aware of any reports of sticking issues with Diprivan stoppers or of any prior art suggesting siliconizing Diprivan stoppers would improve manufacturing efficiency. *Id.* at 29–30 (citing Ex. 2035, 73:6–17, 157:20–25).

We are not persuaded by Patent Owner's argument. It is well settled that "[a] suggestion, teaching, or motivation to combine the relevant prior art teachings *does not have to be found explicitly in the prior art*, as the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references." *In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006) (emphasis added). That the prior art does not include explicit reports of manufacturing issues with Diprivan rubber stoppers in particular is not fatal to Petitioner's argument. We are persuaded by the weight of the evidence that it was understood by a person of ordinary skill in the art that rubber stoppers generally have issues with friction during manufacturing, which is commonly cured by adding silicone oil to the stoppers. *See, e.g.*, Ex. 1004, S4 ("Machinability is greatly improved through the use of lubricated packaging components. Siliconization of rubber products reduces the friction present between the rubber closure and

the metallic machinery."); Ex. 1045, 361 ("Most closures are lightly coated with silicone oil, [which] reduces considerably the inherent tackiness in many rubber formulations. The main advantage of a silicone oil coat is that it facilitates the stoppering operation by lubricating the passage of the closures through assembly machines and insertion into the barrel or vial opening."); Ex. 1002 ¶¶ 20–22.

Moreover, several references offered by Patent Owner teach this same understanding. *See, e.g.*, Ex. 2024, 2:26–37 ("By their nature, elastomeric objects have a relatively high coefficient of friction . . . . This hampers their ability to be transported in filling equipment and similar machinery . . . . In order to overcome this problem, the elastomeric seals in many cases are coated with some lubricant, for instance silicone oil."); Ex. 2040, 1:56–2:6 ("In the prior art, the high coefficient of friction of rubber stoppers and other rubber materials which are being fed to closure devices and other pharmaceutical devices has been the limiting factor in the speed of the machine. . . . One solution which has been proposed to improve the general processibility of rubber closures . . . is the use of silicone oil as a coating on the outside of the stoppers.").

Patent Owner asserts that there can be no motivation to combine prior art references to solve a problem that nobody knows exists. PO Resp. 30–31 (citing *Novartis Pharm. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733, 758 (D. Del. 2014); *Leo Pharms. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013)). But Petitioner did not need to show that there was a known machinability problem with the Diprivan rubber stoppers to establish a reason to combine. *See Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1003 (Fed. Cir. 2016) (agreeing with Petitioner that it "does not need to show that there was a known problem with the prior art system in order to

articulate the required rational underpinning for the proposed combination"). Nevertheless, unlike the cited cases where the art did not appreciate or suggest the existence of the problem, it is clear from the evidence of record that it was known in the art that rubber stoppers generally have manufacturing issues related to their high coefficient of friction, and that those issues are commonly addressed by siliconizing the rubber stoppers.

Accordingly, we find the weight of the evidence sufficient to support Petitioner's argument that a person of ordinary skill in the art would have had a reason to use siliconized rubber stoppers with Diprivan to improve the machinability of those stoppers. *See KSR*, 550 U.S. at 420 ("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.") (emphasis added).

b. Teaching Away

Patent Owner makes a number of arguments as to why a person of ordinary skill in the art would have been discouraged to siliconize the Diprivan rubber stopper. PO Resp. 31–49. We address each argument in turn.

First, Patent Owner asserts that even if a person of ordinary skill in the art would have thought to replace the stopper in Diprivan, "the practical and regulatory burdens in doing so would discourage this type of change." *Id.* at 31–32. In particular, Patent Owner argues that any changes to the approved packaging and manufacturing lines risks significant additional regulatory review. We are not persuaded. "Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291–92 (Fed. Cir. 2013)). We are not

convinced that "risks" of "burdens," or possible application of a "conservative" approach to stopper changes, as they pertain to regulatory review, rise to the level of teaching away. PO Resp. 31–32.

Patent Owner next argues that a person of ordinary skill in the art would have been discouraged from using a siliconized stopper because of safety concerns with silicone oil contamination. *Id.* at 32–49. According to Patent Owner, the dangers of particulate contamination were well known in the art. *Id.* at 34–36. Because of those dangers, the United States and British Pharmacopeias set standards establishing strict limits on particulate contamination in parenteral drug products. *Id.* at 36–37. For emulsions having reduced clarity (like propofol) and that are supplied in containers less than 100 ml, the 2002 British Pharmacopoeia states: "The preparation complies with the test if the average number of particles in the units tested does not exceed 3000 per container equal to or greater than 10 μm and does not exceed 300 per container equal to or greater than 25 μm." Ex. 2047, A257–A258. For emulsions in containers greater than 100 ml, the 2002 British Pharmacopoeia states: "The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per milliliter equal to or greater than 10 μm and does not exceed 2 per milliliter equal to or greater than 25 μm." *Id.* at A257. The U.S. Pharmacopoeia's standard is consistent with the British standard. *See* Ex. 2048, 2729 (Table 2).

Having set forth the standard for acceptable particle contamination, Patent Owner then asserts that several references suggest that siliconized rubber stoppers exceed the limits of contamination, thereby teaching away from the claimed invention. We are not persuaded that the references are as clear as Patent Owner contends. For example, Patent Owner asserts that

Sudo[6] "reports finding 680 particles of 10 μM [sic, μm] per milliliter for the silicone oil treated stopper compared to only 60 such particles for untreated silicone." PO Resp. 41 (citing Ex. 2042). Patent Owner continues, stating "[t]his level of contamination is equivalent to 34,000 particles of 10 μM [sic, μm] in a 50 mL container of Diprivan®, vastly in excess of the [British Pharmacopeia] limit of 3,000 particles of that size." *Id.* (citing Ex. 2036 ¶¶ 72–74).

We disagree with Patent Owner's interpretation of Sudo's data. Sudo teaches that 10 rubber stoppers were added to a bottle containing 300 ml of fine particle-free water. Ex. 2042, 21:59–61. The bottle was then shaken for 60 seconds and allowed to stand for 60 minutes. *Id.* at 21:61–63. The liquid was then flowed through a particle counter to measure the "peeling quantity," which is defined as the "quantity of fine particles, number of particles of 10 μm in diameter (± 3 particles)." *Id.* at 21:63–68, Table 1 n.1. Table 1 indicates that the "Peeling Quantity (Number)" for the siliconized stopper (Comparative Example 2) is 680. *Id.*, Table 1. We, therefore, credit the testimony of Petitioner's declarant, Dr. Feinberg, who testifies that Sudo discloses a *total* of 680 particles of 10 μm in diameter in 300 ml of water. Ex. 1044 ¶ 14; Ex. 2042, Table 1. Thus, 680 particles of 10 μm diameter in 300 ml of water (i.e., 2.3 particles/ml) does not exceed the pharmacopoeia standard of less than 12 particles/ml. *See* Ex. 2047, A257. We, therefore, find that Sudo does not teach away from the use of siliconized rubber stoppers.

[6] Sudo et al., US 5,114,794, issued May 19, 1992 (Ex. 2042).

Patent Owner also argues that Romberg[7] ("the '504 patent"), Thijs[8] ("the '919 patent"), and Mannermaa[9] each teaches away because of their data regarding particle contamination for siliconized rubber stoppers. PO Resp. 42–44. Romberg discloses that the siliconized stoppers placed in 150 ml of filtered deionized water had more than 10,000 particles of 5 μm or more. Ex. 2040, 8:62–9:2. Thijs discloses that the siliconized rubber stoppers, after being in contact with 2 ml of particle free water under steam sterilization conditions, had 50,000 particles of 2 μm or more per ml of fluid. Ex. 2024, Table. And, according to Patent Owner, Mannermaa discloses that siliconized stoppers produced between 1200 and 4500 particles of 5 μm or larger per ml. Ex. 2041, Figure 3.

Having considered the evidence and arguments, we are unable to discern whether the particle contamination results of Romberg, Thijs, and Mannermaa exceed the acceptable amount of particle contamination. The pharmacopoeia standards set forth the acceptable number of particles that are 10 μm in diameter or larger. Ex. 2047, A257–A258; Ex. 2048, 2729 (Table 2). Here, the references each report data that includes particles that are smaller than 10 μm. Thus, the data from the references are not comparable against the pharmacopoeia standard of acceptable contamination.

To show the results for siliconized stoppers are unacceptably high, Patent Owner compares the results with the number of particles for untreated

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[7] Romberg et al., US 4,973,504, issued Nov. 27, 1990 (Ex. 2040).
[8] Thijs et al., US 5,163,919, issued Nov. 17, 1992 (Ex. 2024).
[9] Mannermaa et al., *Comparison of Different Rubber Stoppers; the Effect of Sterilization on the Number of Particles Released*, 46 J. PARENTERAL SCIENCE & TECH. 73–77 (1992) (Ex. 2041).

stoppers and with the number of 5 μm particles reported by Han[10] for a 50 ml container of Diprivan (i.e., 120–200 particles). PO Resp. 42–43. Again, however, we are not persuaded that the data are comparable. According to Han, the 120–200 particles per container represents the properties of "unstressed emulsions." Ex. 1009, Table 1. In contrast, the data reported were from tests conducted in water (Ex. 2040, 8:62–63 (Romberg); Ex. 2024, col. 6 (Table) (Thijs)), and sodium chloride solution (Ex. 2041, 73 (Mannermaa) after agitation and/or sterilization. Moreover, as Petitioner's declarant notes, ten stoppers in a flask would shed more than a single stopper, and a stopper immersed in a solution would shed more than a stopper inserted into a container. Ex. 1044 ¶ 16. In view of those discrepancies, we are not persuaded that any reasonable conclusions can be drawn regarding the number of particles disclosed in the cited references.

Finally, even if a person of ordinary skill in the art reading Sudo or Thijs would be encouraged to use other stoppers over those treated with silicone oil, as Dr. Feinberg agrees (Ex. 2035, 172:7–18, 195:15–197:15), we are not persuaded that this rises to the level of criticizing, discrediting, or discouraging the use of siliconized stoppers in view of what those references teach overall, as discussed above. *Mieresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) ("A reference that 'merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into' the claimed invention does not teach away.") (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731,

[10] Han et al., *Physical Properties and Stability of Two Emulsion Formulations of Propofol*, 215 Intl J. Pharmaceutics 207–220 (2001) (Ex. 1009).

738 (Fed, Cir. 2013)). We, therefore, are not persuaded that the references identified by Patent Owner teach away from the use of siliconized rubber stoppers.

Patent Owner further argues that a person of ordinary skill in the art would be discouraged from using a siliconized rubber stopper with Diprivan because it is an oil-in-water emulsion stabilized by lecithin that would be expected to have a greater propensity for removing silicone oil from a container closure. PO Resp. 44–49. As support for his opinion, Dr. Davis relies on Bae,[11] stating "[t]he potential for hydrogenated lecithin emulsifier to emulsify silicone oil was already known in the prior art." Ex. 2036 ¶ 27 (citing Ex. 2039, Abstract, 526, 527; Ex. 2058 (translation of Bae)). Bae describes the formation of a nanoemulsion with lecithin and silicone oil for cosmetic formulations that has particle sizes of 0.28-0.35 μm. Ex. 2058, 527. Dr. Davis speculates that "[b]ecause any silicone oil emulsified from siliconized rubber closures is not subjected to any mechanical homogenization process, it may form larger droplets relative to the droplets in Diprivan®." Ex. 2036 ¶ 27. We are not persuaded, as Dr. Davis's speculation that larger droplets *may* form is further compounded by the lack of evidence regarding how much silicone oil is leached from the siliconized rubber closures.

[11] Bae et al., *Silicone Nanoemulsion Stabilized with Hydrogenated Lecithin*, 11 J. Korean Ind. Eng. Chem. 522–528 (2000) (Ex. 2039). In this Decision, we cite Exhibit 2058, which is a certified translation of Bae.

Patent Owner relies on Capes[12] and Lomax[13] to demonstrate that Diprivan is capable of removing silicone oil from container closures. PO Resp. 45–47. But the references refer to silicone-lubricated syringes, and not to siliconized rubber stoppers. *See, e.g.*, Ex. 2006, 501 (stating "propofol strips the silicone lubricant from the inside barrel of plastic syringes"); Ex. 2005, 41 (stating silicone oil is sprayed into the syringes by the manufacturers); *see also* Ex. 1044 ¶¶ 25–26. We are not persuaded that an ordinary artisan would have been discouraged from using siliconized stoppers due to results of studies using silicone in the barrel of a syringe. We credit the testimony of Dr. Feinberg, who states that "a person of ordinary skill in the art would have understood that the number of particles shed from a barrel of a plastic syringe would have been significantly higher than the number of particulates shed from one of the ends of a stopper." *See* Ex. 1044 ¶ 27.

Patent Owner also asserts that because Diprivan is heat sterilized, a person of ordinary skill in the art would not use siliconized rubber stoppers given the "unacceptable contamination levels after autoclaving" shown in Mannermaa and Tijs. PO Resp. 47. Petitioner contends that Patent Owner's argument is not commensurate with the scope of the claims because autoclaving is not required by the claims. Pet. Reply 12. We are unaware of any case law that requires the reason to combine to be "commensurate in scope" with the claims, as Petitioner contends. Nevertheless, as explained

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[12] Capes et al., *The Effect on Syringe Performance of Fluid Storage and Repeated Use: Implications for Syringe Pumps*, 50 PDA J. PHARM. SCI. AND TECH. 40–50 (1996) (Ex. 2005).
[13] D. Lomax, *Propofol Injection Pain*, 22 ANESTHESIA AND INTENSIVE CARE 500–501 (1994) (Ex. 2006).

above, we are not persuaded that the data from Mannermaa and Tijs would have discouraged a person of ordinary skill in the art from using a siliconized rubber stopper with Diprivan. Indeed, in the conclusion, Mannermaa recognizes the drawbacks of its study:

> The number of particles released from a stopper during sterilization varies considerably between different stoppers and even between different batches of same stopper. In this study, the whole surface area of the stoppers was studied. In practice only the lower part of the stopper is inside the bottle with the infusion solution. Further studies must be conducted to find out how the stoppers perform in industrial scale facilities with all the process steps used in the LVP production.

Ex. 2041, 77. Moreover, Mannermaa teaches that "[f]urther studies are needed to determine the role of siliconization in the particle-release properties of rubber stoppers." *Id.* Thus, Mannermaa does not discredit or discourage the use of siliconized rubber stoppers; it merely indicates that further studies are recommended.

Patent Owner also argues that a person of ordinary skill in the art "would be particularly concerned about silicone oil contamination in Diprivan® because Diprivan® is intended for use on extremely sick patients, and particulate contamination—even contamination by particles < 5 μM [sic, μm]—was known to be more dangerous for compromised patients." PO Resp. 47–48. We are not persuaded. Although Diprivan is used for critically ill patients, as indicated by the clinical trials described in Diprivan PDR (Ex. 1005, 2940), it is not used exclusively with such patients. Diprivan PDR simply states that Diprivan is "an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation." Ex. 1005, 2939. Patients are anesthetized using Diprivan for a variety of reasons, not just life-threatening ones. Moreover, that Han (and

Patent Owner's declarant, Dr. Davis) found Diprivan contains between 120–200 particles of 5 μm or larger (Ex. 1009, 208) contradicts Patent Owner's argument that a person of ordinary skill in the art would not have used siliconized rubber stoppers because of the risk to extremely sick patients of contamination by particles that are 5 μm or smaller.

Having reviewed the arguments and evidence as a whole, we are not persuaded that the prior art teaches away from the use of siliconized rubber stoppers with Diprivan. Rather, we find that siliconizing Diprivan's rubber stoppers amounts to a combination of familiar elements that yields predictable results. *See KSR*, 550 U.S. at 416 ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

c. Obvious to Try

The Supreme Court set forth the standard for when a combination may be "obvious to try": "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. The Court continued, stating "if this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.*

Petitioner contends that it would have been obvious to try a siliconized rubber stopper with Diprivan. Petitioner argues that "[s]iliconized stoppers were among a handful of possible options for a designer of a parenteral drug packaging system in 2002, and presented an attractive option for those seeking enhanced machinability and ease of use." Pet. 33. Petitioner further argues that although the machinability advantages of silicone coating would have made them the best choice, a person of

ordinary skill in the art would have at least tried silicone coatings as part of the process of seeking the optimal closure given silicone was known to be relatively inert. Pet. 34 (citing Ex. 1002 ¶¶ 20–22); Ex. 1044 ¶¶ 28–31.

Patent Owner asserts that it would not have been obvious to try a siliconized rubber stopper with Diprivan. PO Resp. 49–51. In particular, Patent Owner contends that Petitioner has not explained why a person of ordinary skill in the art would have selected the silicone oil-treated closures. Patent Owner further argues that Petitioner has not identified an existing need or market pressure to explore alternatives to Diprivan's closure, and that there was not a "finite number of identified, predictable solutions." *Id.* at 49–30. Finally, Patent Owner argues that a person of ordinary skill in the art would not have had a reasonable expectation of success because the prior art provided no information regarding the suitability of siliconized bromobutyl closures with a drug like propofol in an oil-in-water emulsion. *Id.* at 50.

Having considered the trial record as a whole, we find Petitioner has the better position. As explained above, it generally was known that rubber stoppers had a high coefficient of friction that resulted in problems with the rubber stoppers sticking to the metallic machinery on automated filling lines. *See, e.g.*, Ex. 1004, S4; Ex. 1045, 361; Ex. 2040, 1:56–68; Ex. 1002 ¶ 20. Although other possible solutions existed (*see, e.g.*, Ex. 1004, S11–S12), the use of silicone oil on the rubber stoppers was repeatedly identified as a solution to that problem. *See, e.g.*, Ex. 1004, S4; Ex. 1045, 361; Ex. 2040, 2:1–6; Ex. 1002 ¶ 21. We credit the testimony of Dr. Feinberg that a person of ordinary skill in the art would have had a reasonable expectation of success in substituting a siliconized rubber stopper for an uncoated rubber stopper. Ex. 1002 ¶ 24. As he explains: "Success, in this context, would

include fewer manufacturing problems compared to uncoated stoppers. It also would have been expected that this substitution would not have resulted in less stability for the emulsion nor in increased propofol degradation." *Id.* As Dr. Feinberg notes, the '010 patent specification refers to "siliconized polymers" as "inert materials," which is a well-known property of silicones. *Id.* (citing Ex. 1001, 9:43–46; Ex. 1013, 66).

Accordingly, because a person of ordinary skill in the art is not an automaton, we find that siliconizing Diprivan's rubber stopper would have been obvious to try with a reasonable expectation of success in light of the inherent stickiness of uncoated rubber stoppers and the known solution to use silicone oil.

d. Dependent Claims

As for the dependent claims, we have considered the arguments and evidence of the complete trial record, and find that Petitioner has shown that each limitation of claims 13–15, 17, 18, 20, and 24–28 is taught by the combination of the cited art. We note, again, that Patent Owner does not contest that the limitations are taught in the prior art.

Claims 13–15 require that the solvent be a water-immiscible solvent (claim 13), such as soybean oil (claims 14 and 15). Diprivan PDR teaches soybean oil as a solvent. Ex. 1005, 2939; Ex. 1002 ¶ 13.

Claim 17 requires that the closure of claim 1 be coated with a material that is inert to propofol. Claim 18 requires that the closure "consists essentially of a material that is itself inert to propofol." And claim 20 requires that the closure comprises siliconized bromobutyl rubber. We find that each of these limitations is taught by van den Heuvel's disclosure of siliconized bromobutyl rubber stoppers, as the siliconized coating is inert to

propofol. Ex. 1010, 4:56–5:1, 5:8–32 (Table A and Table B); Ex. 1002 ¶¶ 18, 22–23; Ex. 1013, 66; Ex. 1001, 9:43–46.

Claims 24–28 recite various stability requirements for the pharmaceutical composition in a container according to claim 1. Petitioner argues that by including 10% soybean oil, as taught in the cited art, the stopper would be non-reactive regardless of the closure selected, and, therefore, the composition suggested by the art necessarily would have had the stability features recited in challenged claims 24–28. Pet. 32–33. Because the claims encompass propofol formulations with 10% soybean oil, and Diprivan PDR teaches that Diprivan comprises 10% soybean oil (Ex. 1005, 2939; Ex. 1002 ¶ 13), we are persuaded that an ordinary artisan would have had a reasonable expectation that siliconizing the bromobutyl stopper of Diprivan would not have resulted in further degradation of the propofol formulation than the unsiliconized bromobutyl stopper. *See* Ex. 1002 ¶¶ 23–24.

Accordingly, we are persuaded that Petitioner has shown that each limitation of the dependent claims is taught by the combination of the cited art. We also find that a person of ordinary skill in the art would have had a reason to use a siliconized bromobutyl rubber stopper with Diprivan for the same reasons stated above.

e. Conclusion as to Obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990) ("After a prima facie case of obviousness has been made and rebuttal evidence submitted, all the evidence must be considered anew."). In doing so, we determine that Petitioner has shown by a preponderance of the evidence that claims 1, 13–

15, 17, 18, 20, and 24–28 are unpatentable as obvious over Diprivan, Farinotti, and van den Heuvel.

E. Obviousness over Diprivan PDR, Farinotti, and Lundgren

Petitioner asserts that claims 1, 13–15, 17, 18, 20, and 24–28 are unpatentable as obvious over Diprivan PDR, Farinotti, and Lundgren. Pet. 34–38. Patent Owner opposes Petitioner's assertion for substantially the same reasons stated above. PO Resp. 23–51. We incorporate here our earlier findings and discussion regarding the disclosures of Diprivan PDR and Farinotti. Based on the complete record, we determine that Petitioner has established by a preponderance of the evidence that claims 1, 13–15, 17, 18, 20, and 24–28 are unpatentable as obvious over the cited art.

1. Lundgren (Ex. 1031)

Lundgren relates to solutions of low molecular weight thrombin inhibitors stored in primary packages containing rubber components, such as vials, bottles, cartridges, and prefilled syringes. Ex. 1031, 1:5–7. In particular, Lundgren states that it has "surprisingly been found that by using rubber material containing bromobutyl instead of chlorobutyl, the stability of the low molecular weight thrombin inhibitors in solution can be considerably improved." *Id.* at 1:21–23. Lundgren also discloses the use of both unsiliconized and siliconized stoppers, including the use of a siliconized bromobutyl rubber closure. *Id*. at 11:1–13:11.

2. Analysis

Petitioner's arguments with respect to this ground are largely the same as above, with the exception that Petitioner relies on Lundgren instead of van den Heuvel for its disclosure of a siliconized bromobutyl rubber stopper. Pet. 35–38. Petitioner also asserts that Lundgren "taught that the siliconized bromobutyl rubber closure imparted greater stability to the pharmaceutical

composition than did unsiliconized bromobutyl rubber closures." *Id.* (citing Ex. 1031, 11–12). Finally, Petitioner asserts that the motivation to combine Diprivan PDR, Farinotti, and Lundgren "is essentially the same as that presented for Ground 1." Pet. 36.

We are persuaded, for the same reasons stated above, that Petitioner has shown that the combination of Diprivan PDR and Farinotti teaches each limitation of claims 1, 13–15, 17, 18, 20, and 24–28 except a siliconized bromobutyl rubber stopper, which is taught by Lundgren (*see* Ex. 1031, Abstract, 10:13–19, 28–30, 11:1–3). We are also persuaded, for the same reasons stated above, that a person of ordinary skill in the art would have had a reason to use a siliconized bromobutyl rubber stopper with Diprivan given the known benefits of doing so.

Patent Owner makes largely the same arguments in opposition to this challenge. That is, Patent Owner argues that a person of ordinary skill in the art would not have had a reason to use siliconized bromobutyl rubber stoppers with Diprivan. For example, Patent Owner argues that an ordinary artisan would not have combined the siliconized bromobutyl stoppers of Lundgren because it concerns an aqueous product rather than an oil-in-water emulsion. PO Resp. 26–28. We agree with Patent Owner and are not persuaded that Lundgren teaches that "the siliconized bromobutyl rubber closure imparted greater stability to the pharmaceutical composition than did unsiliconized bromobutyl rubber closures," as Petitioner asserts. *See* Pet. 35. Based on the results cited by Petitioner, Lundgren concluded that "[m]elagatran in water solution of NaCl exhibits a somewhat lower degradation compared to melagatran in water solution of HPβCD." Ex. 1031, 13. Thus, Lundgren says nothing about the stability imparted by siliconized versus unsiliconized closures, particularly given some of the

results of unsiliconized stoppers (e.g., Sample E2) were the same as that of siliconized stoppers (e.g., Sample F2). *Id.* at 12.

Nevertheless, for the same reasons stated above, we are persuaded that the manufacturing benefits of siliconizing rubber stoppers would have provided a person of ordinary skill in the art a reason to use a siliconized bromobutyl rubber stopper with Diprivan with a reasonable expectation of success. We are also persuaded that the prior art did not teach away from the use of siliconized bromobutyl rubber stoppers with Diprivan. Finally, we are persuaded that a person of ordinary skill in the art would have found it obvious to try a siliconized bromobutyl rubber stopper with Diprivan.

Accordingly, having evaluated all of the evidence together, we determine that Petitioner has shown by a preponderance of the evidence that claims 1, 13–15, 17, 18, 20, and 24–28 are unpatentable as obvious over Diprivan PDR, Farinotti, and Lundgren. *See In re Eli Lilly*, 902 F.2d at 945.

III. CONCLUSION

We conclude that Petitioner has established by a preponderance of evidence that claims 1, 13–15, 17, 18, 20, and 24–28 of the ’010 patent are unpatentable as obvious.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 13–15, 17, 18, 20, and 24–28 of the ’010 patent are unpatentable as obvious over Diprivan PDR, Farinotti, and van den Heuvel;

FURTHER ORDERED that claims 1, 13–15, 17, 18, 20, and 24–28 of the ’010 patent are unpatentable as obvious over Diprivan PDR, Farinotti, and Lundgren;

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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