

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NALOX-1 PHARMACEUTICALS, LLC,
Petitioner,

v.

OPIANT PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00685
Patent 9,211,253 B2

Before ZHENYU YANG, JACQUELINE T. HARLOW, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

INTRODUCTION

Nalox-1 Pharmaceuticals, LLC (“Petitioner”) filed a Petition (Paper 1 (“Pet.”)), seeking an *inter partes* review of claims 1–29 of U.S. Patent 9,211,253 B2 (“the ’253 patent,” Ex. 1001). Opiant Pharmaceuticals, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

Under the statute, an *inter partes* review may not be instituted unless the information presented in the petition and the preliminary response shows “there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision under § 314 may not institute review on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018).

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Thus, based on the information presented, and under *SAS*, we institute an *inter partes* review of claims 1–29 of the ’253 patent.

Related Proceedings

Petitioner concurrently filed IPR2019-00686 and IPR2019-00687, challenging the same claims of the ’253 patent with additional prior art.

The ’253 patent is one of five patents listed in the Orange Book for intranasal naloxone sold under the brand name NARCAN. Pet. 1; Paper 8, 1. Petitioner also filed petitions for *inter partes* review, challenging the other four patents listed. Pet. 6; Paper 5, 1–2.

According to the parties, Patent Owner asserted all five Orange-Book-listed patents in *Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc.*, Case 2:16-cv-07721 (D.N.J.) (consolidated, “the Teva Case”),

and *Adapt Pharma Operations Ltd. v. Perrigo UK FINCO Limited Partnership*, Case 2:18-cv-15287 (D.N.J.). Pet. 5; Paper 5, 2. Petitioner is not involved in those actions. Pet. 5–6.

Background of Technology and the '253 Patent

Opioid overdose is a crisis in the United States. Ex. 1001, 6:34. Naloxone is an opioid receptor antagonist that was initially approved for use by injection for the reversal of opioid overdose. *Id.* at 2:9–10. Naloxone hydrochloride injection prevents or reverses the effects of opioids, “including respiratory depression, sedation and hypotension.” Ex. 1044,¹ 1300.

According to the '253 patent, administering naloxone via injection requires trained medical personnel and imposes the risk of exposure to blood borne pathogens through needlestick injury. Ex. 1001, 6:10–22. The '253 patent discloses that “it ha[d] been suggested that in view of the growing opioid overdose crisis in the US, naloxone should be made available over-the-counter (OTC), which would require a device, such as a nasal spray device, that untrained consumers are able to use safely.” *Id.* at 6:33–37.

The '253 patent acknowledges that nasal administration of naloxone was known and used by numerous medical services and health departments. Ex. 1001, 2:25–6:3, *see also id.* at 4:32–35 (“Overdose education and nasal naloxone distribution (OEND) programs are community-based interventions that educate people at risk for overdose and potential bystanders on how to

¹ Physicians' Desk Reference 2003, entry for NARCAN (Naloxone Hydrochloride Injection, USP).

prevent, recognize and respond to an overdose.”). It points out, however, although some studies “reported that the nasal administration of naloxone is as effective as the intravenous route in opiate addicts,” others “reported that naloxone administered intranasally displays a relative bioavailability of 4% only and concluded that the IN [intranasal] absorption is rapid but does not maintain measurable concentrations for more than an hour.” *Id.* at 2:45–51.

The ’253 patent states

Thus, there remains a need for durable, easy-to-use, needleless devices with storage-stable formulations, that can enable untrained individuals to quickly deliver a therapeutically effective dose of a rapid-acting opioid antagonist to an opioid overdose patient. The therapeutically effective dose should be sufficient to obviate the need for the untrained individual to administer either a second dose of opioid antagonist or an alternative medical intervention to the patient, and to stabilize the patient until professional medical care becomes available.

Id. at 6:43–52.

According to the ’253 patent, its invention relates to devices adapted for nasal delivery of “a therapeutically effective amount of an opioid antagonist selected from naloxone and pharmaceutically acceptable salts thereof, wherein the device is pre-primed, and wherein the therapeutically effective amount, is equivalent to about 2 mg to about 12 mg of naloxone hydrochloride.” *Id.* at 6:54–60.

Illustrative Claim

Among the challenged claims, claim 1 is independent, and is reproduced below:

1. A single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single

reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:
about 4 mg naloxone hydrochloride or a hydrate thereof;
between about 0.2 mg and about 1.2 mg of an isotonicity agent;
between about 0.005 mg and about 0.015 mg of a preservative;
about 0.2 mg of a stabilizing agent;
an amount of an acid sufficient to achieve a pH o[f] 3.5-5.5.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims	Basis	References
1-3, 16-24, 28, 29	§ 103(a)	Wyse ² and HPE ³
4-7, 10-15, 25-27	§ 103(a)	Wyse, Djupesland, ⁴ and HPE
8, 9	§ 103(a)	Wyse, Djupesland, HPE, and the '291 patent ⁵

In support of its patentability challenge, Petitioner relies on the Declarations of Maureen D. Donovan, Ph.D. (Ex. 1002) and Günther Hochhaus, Ph.D. (Ex. 1003).

ANALYSIS

Discretion under § 314(a)

Under § 314(a), the Director has discretion to deny institution of an *inter partes* review. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) (“[T]he agency’s decision to deny a petition is a matter

² Wyse et al., U.S. Patent 9,192,570 B2, issued November 24, 2015 (Ex. 1007).

³ Handbook of Pharmaceutical Excipients, 56-60, 64-66, 78-81, 220-22, 242-44, 270-72, 441-45, 517-22, 596-98 (Rowe et al. eds., 6th ed. 2009) (Ex. 1012).

⁴ Djupesland, *Nasal Drug Delivery Device: Characteristics and Performance in a Clinical Perspective - A Review*, 3 DRUG DELIV. & TRANSL. RES. 42-62 (2013) (Ex. 1010).

⁵ Wermeling, U.S. Patent 8,198,291 B2, issued June 12, 2012 (Ex. 1015).

committed to the Patent Office’s discretion.”). Citing *NHK Spring Co. v. Intri-Plex Techs. Inc.*, IPR2018-00752, Paper 8 (PTAB Sept. 12, 2018) (precedential), Patent Owner asks us to deny the Petition in light of the parallel district-court actions. Prelim. Resp. 5–15. We decline to do so for the following reasons.

In *NHK*, the Board exercised its discretion under 35 U.S.C. §§ 314(a) and 325(d) to deny institution of an *inter partes* review. *NHK*, IPR2018-00752, Paper 8, 2. For the analysis under § 314(a), the Board considered “the status of the district court proceeding *between* the parties,” and concluded that “the advanced state of the district court proceeding is an additional factor that weighs in favor of denying the Petition under § 314(a).” *Id.* at 19–20 (emphasis added).

Here, Patent Owner represents that “Teva, a motivated pharmaceutical company who has recently obtained FDA approval for its generic intranasal naloxone product, filed a Paragraph IV certification challenging the same patents and is currently litigating the Teva Case in the District of New Jersey.” Prelim. Resp. 11. It is undisputed that Petitioner is not involved in the Teva Case. *Id.* at 12; Pet. 5–6.

Additionally, the petitioner in *NHK* asserted “the same prior art and *arguments*” in both the district-court proceeding and the IPR petition. *NHK*, IPR2018-00752, Paper 8, 20 (emphasis added). Here, Patent Owner contends that the Teva Case “involves the *same* prior art references as those asserted by Petitioner in this proceeding.” Prelim. Resp. 11. Patent Owner, however, does not proffer evidence to show, or even assert, that the arguments presented by Petitioner in this proceeding are the same or

substantially similar to those at issue in the Teva Case. Thus, the facts in this case are distinguishable from those in *NHK*.

In addition, as explained below, Petitioner has presented evidence supporting its challenge of claims 1 and 16–24, including that Wyse discloses a range of naloxone doses that fully encompasses the dosage recited in claim 1, thereby establishing a presumption of obviousness. That presumption, coupled with the fact that the only other arguments Patent Owner raises to oppose institution are premised on limitations not found in claims 1 and 16–24, further distinguishes the facts here.

Patent Owner also argues that “under similar circumstances to this Petition, where a parallel district court action was pending against a generic pharmaceutical company unrelated to the petitioner, the Board recently declined to institute a petition.” Prelim. Resp. 12 (citing *Neptune Generics, LLC v. Aventis Generics S.A.*, IPR2019-00136, Paper 15 (PTAB May 6, 2019), 35–37). “In that case,” Patent Owner continues, “like this one, the parallel court proceedings involved the same invention and the same prior art, but did not involve the IPR petitioner.” *Id.* The facts here are also distinguishable from those in *Neptune*.

In *Neptune*, the Board exercised its discretion under § 325(d) to deny institution, because the prior art and arguments in that petition were substantially similar to those presented in a prior IPR petition challenging the same claims of the same patent. *Neptune*, IPR2019-00136, Paper 15, 30–35. It was within this context that the Board considered the district-court action “as an adjunct to” its analysis under § 325(d). *Id.* at 35. In other words, the Board did not deny the petition solely based on the parallel district-court proceeding.

Moreover, at the time the Board denied institution in *Neptune*, the district court had completed a bench trial and concluded that the same challenged claims had not been shown to be invalid. *Id.* at 23. That decision was appealed, and was ready for oral argument before the Federal Circuit. *Id.* at 25. In contrast, here, although the Teva Case is “nearing its final stages,” trial just started and the district court has not entered any judgment concerning the validity of the ’253 patent claims. Prelim. Resp. 11; *see also* Paper 10 (noting a bench trial is scheduled to begin on August 26, 2019). This distinction is significant because the parties to the Teva Case may settle, and the district court may dismiss the case without adjudicating the merits.

In short, under the circumstances of this case, we decline to deny the Petition in view of the parallel district court actions involving the ’253 patent.

Consistent with the guidance provided in the July 2019 Update to the Office Trial Practice Guide,⁶ we sought and received briefing from the parties concerning the relative strength of and differences between the three parallel petitions filed by Petitioner against the ’253 patent. Papers 7–9. In its filing ranking the three parallel petitions, Petitioner asks that we consider the Petition in the instant proceeding first. Paper 8, 1. For the reasons given herein, we conclude in the instant proceeding that Petitioner has established a reasonable likelihood of prevailing in demonstrating the unpatentability of

⁶ Office Patent Trial Practice Guide, July 2019 Update, 84 Fed. Reg. 33,925 (July 16, 2019) (“Trial Practice Guide Update”), <https://www.uspto.gov/sites/default/files/documents/trial-practice-guide-update3.pdf>, 27 n.4.

at least one claim of the '253 patent. We address in separate decisions Petitioner's less preferred petitions, IPR2019-00686 and IPR2019-00687.

Level of Ordinary Skill in the Art

Petitioner argues that “[a]s it relates to the '253 patent, a person of ordinary skill in the art (‘POSA’) would comprise a team of individuals having experience in drug development, and specifically the development of solution-based dosage forms such as intranasal dosage forms.” Pet. 7 (citing Ex. 1002 ¶ 26; Ex. 1003 ¶ 22).

According to Petitioner, this team would include a “Formulator POSA” who has “experience in preformulation testing for and selection of excipients for a solution-based dosage form (including intranasal dosage forms) to achieve a target pharmaceutical profile.” *Id.* at 7.

This team, Petitioner asserts, would also include a “Pharmacologist POSA,” who has “clinical, clinical pharmacology, and regulatory expertise relevant to the design and performance of a drug development strategy for solution-based dosage forms such as intranasal dosage forms, including testing and/or evaluating the fate of the drug in the body (i.e., pharmacokinetics, including the physiological and biopharmaceutical aspects of nasal drug absorption), testing and/or evaluating issues of safety and efficacy, and evaluating the regulatory requirements of a new dosage form.” *Id.* at 8.

For purposes of this Decision, Patent Owner does not dispute, and we adopt, Petitioner's proposed definition of the level of ordinary skill.

Claim Construction

In an *inter partes* review, a claim term “shall be construed using the same claim construction standard that would be used to construe the claim in

a civil action under 35 U.S.C. [§] 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (holding that the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application”) (citations omitted). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes that we construe certain terms. Pet. 22–23. On this record and for purposes of this Decision, we see no need to construe any term expressly. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (stating that claim terms need only be construed to the extent necessary to resolve the controversy).

Obviousness over Wyse and HPE

Petitioner argues that claims 1–3, 16–24, 28, and 29 would have been obvious over Wyse and HPE. Pet. 28–45. Based on this record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion, at least with regard to claims 1 and 16–24.

Wyse issued on November 24, 2015, from an application filed on December 19, 2014. Ex. 1007, (22), (45). Petitioner asserts that the earliest priority date for challenged claims is March 16, 2015. Pet. 10–12. Thus, Petitioner argues that Wyse qualifies as prior art under AIA § 102(a)(2). *Id.*

at 24. For the purposes of this proceeding, Patent Owner does not dispute, and we agree with, Petitioner’s argument on this point. Paper 9, 1.

Wyse teaches “compositions containing an opioid antagonist such as naloxone and one or more pharmaceutically acceptable excipients. The compositions may be used for intranasal delivery of Naloxone for the treatment of, for example, opioid overdose in an individual in need thereof.” Ex. 1007, Abstract. HPE lists pharmaceutical excipients, including benzalkonium chloride,⁷ benzyl alcohol, and disodium edetate (EDTA). Ex. 1012. HPE describes various information of each excipient, such as the applications in pharmaceutical formulation as well as safety. *Id.*

Claims 1 and 16–24

Regarding challenged claim 1, Petitioner argues that Wyse teaches all but one limitation (Pet. 28–34), and HPE teaches that missing limitation: “between about 0.005 mg and about 0.015 mg of a preservative” (*id.* at 31–33). Patent Owner relies on, among other evidence, the Declaration of Kenneth A. Williams, M.D. (Ex. 2001), and focuses its rebuttal on the limitation requiring “about 4 mg naloxone hydrochloride or a hydrate thereof,” arguing that Wyse does not teach, and an ordinary artisan would not have been motivated to use, intranasal naloxone in a single dose of 4 mg. Prelim. Resp. 17–48. Based on the current record, and for the following reasons, we find Petitioner’s arguments more persuasive. Patent Owner does not dispute that the combination of Wyse and HPE teaches or suggests the other limitations of claim 1. Because we find Petitioner has met its

⁷ Benzalkonium chloride is abbreviated as BAC in the Petition, and BZK in the Preliminary Response.

burden at this stage of the proceeding with respect to those limitations, we focus our discussion on the limitation of dosage amount.

In an IPR, an overlap between the ranges of a claimed composition and those disclosed in the prior art creates a presumption of obviousness. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). In this case, Wyse teaches “compositions comprising naloxone for intranasal delivery.” Ex. 1007, 3:41–42. As Petitioner points out, Wyse states that “the disclosed compositions may comprise from about 5 mg/mL to about 50 mg/mL . . . of an opioid antagonist.” Pet. 30 (citing Ex. 1007, 6:50–65). According to Wyse, “[t]he opioid antagonist may be naloxone or a pharmaceutically acceptable salt thereof.” Ex. 1007, 6:59–60, *see also id.* at 6:62–65 (defining “naloxone” as “refer[ring] to naloxone, naloxone HCl, naloxone HCl dihydrate, any pharmaceutically acceptable salt of naloxone, or combinations thereof”). Wyse also teaches the Aptar/Pfeiffer Unitdose delivery device, which delivers a volume of about 100 μ L per spray, may be used to deliver the intranasal naloxone composition. *Id.* at 10:53–56. Thus, we agree with Petitioner that “Wyse discloses an amount of about 0.5 mg to 5 mg naloxone hydrochloride or naloxone hydrochloride dihydrate in 100 μ L of solution.” *See* Pet. 30–31 (citing Ex. 1002 ¶ 126). This range fully encompasses the dosage of “about 4 mg naloxone hydrochloride or a hydrate thereof” in challenged claim 1. As a result, we are persuaded that there is a presumption of obviousness.

Patent Owner asserts that “the range of ‘from about 5 mg/mL to about 50 mg/mL’ does not refer specifically to naloxone.” Prelim. Resp. 40. We disagree. Wyse claims a nasal spray composition comprising “from about 5 mg/mL to about 50 mg/mL of naloxone.” Ex. 1007, claims 1 and 15, *see*

also id. at 8:54–58 (disclosing an aseptic composition comprising “from 5 mg/mL to 50 mg/mL of an opioid antagonist selected from naloxone, naloxone HCl, naloxone HCl dihydrate, or a combination thereof”).

Patent Owner also contends that “the teaching of ‘from about 5 mg/mL to about 50 mg/mL’ refers to a concentration, not to a dose and that disclosure is not tied to a volume of 100 μ L, or for that matter, any particular volume.” Prelim. Resp. 40. Patent Owner points out that Wyse teaches modifying the nasal spray device to deliver “between 50 μ L to about 200 μ L spray.” *Id.* at 40–41 (citing Ex. 1007, 10:39–41). According to Patent Owner, 50 μ L of spray with a concentration of 50 mg/mL would lead to 2.5 mg, and not 4 mg, naloxone. *Id.* Arithmetically, Patent Owner is correct. But, the modified volume range emphasized by Patent Owner only broadens the dosage range from “0.5 to 5 mg” argued by Petitioner to “0.25 mg (50 μ L of 5 mg/mL) to 10 mg (200 μ L of 50 mg/mL),” which would still encompass the claimed “about 4 mg” dosage, and thus, create a presumption of obviousness.

According to Patent Owner, “Petitioner’s error is compounded, moreover, by Wyse’s express teaching that the volume could be administered as ‘half doses’ to two nostrils.” Prelim. Resp. 41 (citing Ex. 1007, 11:16–17). Wyse teaches:

In another aspect, the unit dose comprises about 200 μ L of a disclosed composition, where the unit dose may be divided into two half doses. Each half dose may comprise about 100 μ L of a disclosed composition, such that administration of the two half doses results in a total administration of about 200 μ L of the composition.

Ex. 1007, 11:15–20. When read in context, each half dose is 100 μ L, the volume Petitioner relies on to calculate the dosage amount. Thus, the passage Patent Owner relies on does not support its position.

In view of Wyse’s teaching of a nasal spray composition comprising from about 5 mg/mL to about 50 mg/mL of naloxone, delivered in a 100 μ L unit dose, we determine Petitioner has established a presumption of obviousness of challenged claim 1. Patent Owner argues that Petitioner has not carried its burden to show that a concentration of 40 mg/mL is desirable for naloxone itself. Prelim. Resp. 40. We are not persuaded by this argument. As explained above, Wyse claims a nasal spray composition comprising “from about 5 mg/mL to about 50 mg/mL of naloxone.”

Moreover,

[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.

Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 737–38 (Fed. Cir. 2013). A patentee may also rebut the presumption of obviousness created by an overlapping range by showing that “a change to a parameter may be patentable if the parameter was not recognized as ‘result-effective,’” or that range disclosed in the prior art is especially broad. *DuPont*, 904 F.3d at 1006.

Here, Patent Owner has presented certain evidence and arguments that amount to an effort to rebut the presumption. For example, Patent Owner argues that an ordinary artisan would not have been motivated to use a single intranasal naloxone dose of 4 mg. Prelim. Resp. 17–48. According to

Patent Owner, higher doses of naloxone risked withdrawal symptoms and other negative effects. *Id.* at 26–37 (citing Ex. 2001 ¶¶ 26–36). Although we recognize “[t]he concerns about withdrawal . . . are not mere conjecture” (*id.* at 35), it appears “opiate withdrawal is not a medical emergency,” and is described as “moderate to severe flu-like illness, subjectively severe but objectively mild” (Ex. 1049, 60:3–6). Meanwhile, “[s]erious complications (seizure, pulmonary oedema, asystole, cardiac arrest) after naloxone administration are reportedly rare (0.3 and 1.6%).” Ex. 1035, 381.

Patent Owner also contends that an ordinary artisan would not have been motivated to use an initial intranasal dose of 4 mg because the prior art taught that 2 mg or less was therapeutically effective. Prelim. Resp. 20–23. According to Patent Owner, “*all* of the lengthy list of clinical references with which the POSA would have been familiar—many of which Petitioner cited, *see, e.g.*, Pet. at 14–15—involved doses of 2 mg naloxone *or less.*” *Id.* at 21 (citing Ex. 2001 ¶ 38). Patent Owner’s argument is not unreasonable. But, although it appears these references all involved the administration of an initial dose of 2 mg or less, it is unclear whether any “criticize[d], discredit[ed], or otherwise discourage[d]” increasing that dose to above 2 mg. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Moreover, at least one of the references reports that twice as many of the patients who received an initial dose of intranasal naloxone (IN) “were given second doses” as compared to patients who received intravenous naloxone (IV), and suggests “this finding may represent the need for a higher naloxone dose when given IN, rather than IV.” Ex. 1040, 8.

Patent Owner also challenges “[t]he purported motivation to administer a 4 mg dose aris[ing] from a calculation that Petitioner performs

using pharmacokinetic data disclosed in Table 4 of Wyse.” Prelim. Resp. 45. For that calculation, Petitioner argues “prior art concentrated intranasal naloxone formulations had bioavailability of about 40% as compared to injectable naloxone.” Pet. 18 (citing Ex. 1002 ¶ 53; Ex. 1003 ¶ 59; Ex. 1007, Table 4). Relying on the FDA’s requirement that “an intranasal naloxone formulation to meet or exceed the exposure levels of an approved dose of the injection,” Petitioner argues that an ordinary artisan would have, “[b]ased on simple math,” arrived at an intranasal formulation with 4–6 mg naloxone to match the exposure levels of 2 mg, the highest FDA-approved initial injection dosage. *Id.* at 18–19 (citing Ex. 1002 ¶ 56; Ex. 1003 ¶ 61; Ex. 1032, 8, 14–15; Ex. 1049, 166, 169–70, 172).

Patent Owner does not dispute that, in 2012, the FDA required “an intranasal naloxone formulation for community use match or exceed the exposure of an FDA-approved parenteral product.” Prelim. Resp. 34. Patent Owner, however, again contends that before the ’253 patent, an ordinary artisan would not have chosen the highest FDA-approved intravenous naloxone dose because of concerns about withdrawal. *Id.* at 43. In addition, Patent Owner appears to question Petitioner’s approach in calculating the bioavailability of intranasal naloxone. *See id.* at 45 (“Petitioner’s experts assume dose-linearity and then appear to have used the ‘AUC’ (area-under-the-curve) data for these three formulations to calculate intranasal bioavailability of about 36% for 1 mg IN and about 42% for 2 mg IN.”) (citing Ex. 1003 ¶ 59).

We share Patent Owner’s doubt over Petitioner’s assertion that the relative bioavailability of intranasal naloxone is 40%. Indeed, several references Petitioner relies on show “i.n. route to have similar

pharmacokinetics to the i.v. route with 100% bioavailability.” Ex. 1035, 382; *see also* Ex. 1021, 267 (“After intranasal mucosal administration, naloxone exhibits opiate antagonist effects almost as rapidly as the i.v. route with a bioavailability and clinical response approaching 100% in animal and human studies.”). These numbers conflict with Petitioner’s calculated bioavailability of 40%.

Moreover, as Patent Owner points out, Petitioner admits that “as expected from the prior art, a more concentrated intranasal naloxone solution has been shown to have a higher bioavailability.” Prelim. Resp. 25 (quoting Ex. 1003 ¶ 59). Based on that logic, even if Petitioner is correct that the relative bioavailability of intranasal naloxone at 10 mg/ml is 40%, a more concentrated naloxone solution would also have higher bioavailability. This casts further doubt over the premise for Petitioner’s “simple math” in calculating intranasal naloxone of 4–6 mg. Nevertheless, these factual issues, together with evidence of secondary considerations, are better suited for evaluation after the parties fully develop the record during trial.

Petitioner also argues that claims 16–24 would have been obvious over Wyse and HPE. Pet. 39–43. Patent Owner does not address these claims separately. After considering the Petition, the Preliminary Response, and accompanying evidence, we are persuaded that, for purposes of this Decision, Petitioner has made a sufficient showing regarding the unpatentability of those claims.⁸

⁸ Patent Owner asserts that “[c]laims 2–15 and 17–29—in other words all except two of the claims in the ’253 patent—require” benzalkonium chloride as a preservative and EDTA as a stabilizing agent. Prelim. Resp. 49. Patent Owner is mistaken. Claims 17–24 do not require so.

Having determined that Petitioner has demonstrated a reasonable likelihood of showing the unpatentability of claims 1 and 16–24, we institute an *inter partes* review as to all claims challenged in the Petition. *See SAS*, 138 S. Ct. at 1355–56; *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”). We nevertheless offer the following observations on Petitioner’s challenges of the other claims.

Claims 2, 3, 28, and 29

Claim 2 depends from claim 1, and further recites “the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid.” Claims 3, 28, and 29 depend, directly or indirectly, from claim 2. Petitioner argues that Wyse teaches using NaCl, EDTA, and hydrochloric acid. Pet. 35–36. Relying on HPE, Petitioner also asserts that an ordinary artisan “would have been particularly motivated to use benzalkonium chloride (‘BAC’) as a preservative in such a nasal spray, as it is a commonly used antimicrobial preservative in FDA-approved nasal formulations that has a broad range of antimicrobial activities at low concentrations, such as 0.002-0.02 % w/v.” *Id.* at 33 (citing Ex. 1012, 56; Ex. 1002 ¶¶ 64, 137), 35 (the same). Patent Owner counters that the prior art teaches away from using the combination of benzalkonium chloride and EDTA. Prelim. 49–59. We find Patent Owner’s arguments more persuasive.

“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). In its preliminary formulation screening studies, Wyse evaluated 13 excipient combinations. Ex. 1007, 26:26–27. According to Wyse, the results “surprisingly showed that the use of benzalkonium chloride, a common nasal product preservative, resulted in an additional degradant in formulations 7, 9, 14, and 14A.” *Id.* at 27:29–32. Wyse concluded that “benzyl alcohol and paraben preservatives were acceptable, but benzalkonium chloride was not, due to increased observed degradation.” *Id.* at 27:42–44. This explicit statement—despite Petitioner’s contention that Wyse did not “conclusively determine[] that any individual excipient was responsible for any instability issues in the disclosed formulation” (Pet. 55)—appears to directly “criticize, discredit, or otherwise discourage the solution claimed.” *See In re Fulton*, 391 F.3d at 1201. Thus, we agree with Patent Owner that Wyse teaches away from using benzalkonium chloride as an excipient here. *See Prelim. Resp.* 50–51.

Petitioner questions whether, in Wyse, benzalkonium chloride “specifically resulted in additional naloxone degradation, rather than degradation of another component.” Pet. 55. We are not persuaded. Indeed, Wyse singled out benzylalkonium chloride as one of the commonly used excipients that “increase *degradation of naloxone*.” Ex. 1007, 28:23–27, *see also id.* at 27:19–21 (discussing the “stability of naloxone HCl” and “degradation of naloxone HCl”).

Petitioner also points out that formulation 12 of Wyse includes benzylalkonium chloride, “but was not disclosed to result in additional degradants.” Based on the current record, we are not persuaded by this argument either. Each of claims 2, 3, 28, and 29 requires not only

benzylalkonium chloride as the preservative, but also EDTA as the stabilizing agent. As Patent Owner points out, formulation 12 combines benzylalkonium chloride with “a number of other excipients, *but not EDTA.*” Prelim. Resp. 55 (citing Ex. 1007, Table 13). Instead, Wyse reports all three of the formulations containing both benzylalkonium chloride and EDTA (formulations 7, 14, and 14A) were unstable. *Id.* at 49 (citing Ex. 1007, Table 13, 27:29–32, Table 14). Thus, including benzylalkonium chloride in formulation 12 does not negate Wyse’s explicit statement discrediting it as an excipient in intranasal naloxone formulation.

Petitioner further contends that ordinary artisans “reading the disclosure of Wyse have concluded that it does not teach away” from using benzalkonium chloride. Pet. 55. As support, Petitioner cites Glende,⁹ “a Norwegian graduate thesis published in 2016.” *Id.* Acknowledging that Glende is not prior art, Petitioner nevertheless points out that Glende “reviewed the WIPO publication equivalent of Wyse [and] not[ed] that the disclosure should not be understood to disparage the use of BAC, as the criticism of its use may be incorrectly based.” *Id.* at 55–56 (citing Ex. 1031, 76¹⁰). Petitioner, however, neglected to mention that Glende also reviewed the WIPO publication equivalent of the challenged ’253 patent (Ex. 1031, 54), and noted that the formulations disclosed therein, which included benzalkonium chloride, were “storage-stable” (*id.* at 64). After reviewing

⁹ Glende, O., *Development of Non-Injectable Naloxone for Pre-Hospital Reversal of Opioid Overdose: A Norwegian Project and a Review of International Status* (May 2016) (unpublished M.A. thesis, Norwegian University of Science and Technology).

¹⁰ The parties cite to the original page numbers of the thesis, and not the Exhibit. For the sake of consistency, we do the same.

the thesis, we agree with Patent Owner that “Glende’s statement that BZK ‘should not be depreciated based on [Wyse] solely,’ *id.* at 76—the very point for which Petitioner tries to use it—was thus *based on knowledge of the patented invention.*”

In sum, the evidence currently of record supports Patent Owner’s position that in view of its teachings as a whole, Wyse teaches away from using benzylalkonium chloride, and especially with EDTA, in formulating intranasal naloxone.

Patent Owner argues that, in addition to Wyse, HPE also teaches away from using benzylalkonium chloride and EDTA together, as required in challenged claims 2–15 and 25–29. Prelim. Resp. 56–59. For the following reasons, we find this argument persuasive too.

Petitioner asserts that HPE teaches using benzylalkonium chloride in nasal formulations. Pet. 35 (citing Ex. 1012, 56). Petitioner, however, ignores that HPE specifically teaches that “[n]asal formulations containing benzalkonium chloride and disodium edetate, both known to be local irritants, were shown to produce an inflammatory reaction, and microscopic examination showed an extended infiltration of the mucosa by eosinophils, and pronounced atrophy and disorganization of the epithelium”

Ex. 1012, 243.

As Petitioner acknowledges, “minimizing irritation” is an important consideration in selecting excipients for intranasal naloxone formulation. Pet. 20. Thus, we agree with Patent Owner that HPE’s teaching that both benzylalkonium chloride and EDTA are “known to be local irritants,” and using them together with would “produce an inflammatory reaction” would

have discouraged an ordinary artisan from doing so. *See* Prelim. Resp. 58–59.

In conclusion, based on the current record, we find both Wyse and HPE teach away from using benzylalkonium chloride and EDTA together in intranasal naloxone formulation. Because claims 2, 3, 28 and 29 require benzalkonium chloride as the preservative and EDTA as the stabilizing agent, Petitioner has not shown a reasonable likelihood in prevailing in its assertion that these claims would have been obvious over Wyse and HPE. Nevertheless, under *SAS*, because we institute an *inter partes* review of claims 1 and 16–24, we institute review of all claims challenged under this ground.

Other Grounds

Petitioner argues that (1) claims 4–7, 10–15, and 25–27 would have been obvious over Wyse, Djupesland, and HPE (Pet. 45–52), and (2) claims 8 and 9 would have been obvious over Wyse, Djupesland, HPE, and the '291 patent (*id.* at 52–54). All the claims challenged under these two grounds depend, directly or indirectly, from claim 2, which requires the combination of BZK as the preservative and EDTA as the stabilizing agent. As explained above, based on the current record, we find Patent Owner's teaching-away arguments persuasive. Nevertheless, under *SAS*, we institute an *inter partes* review of all claims challenged under all grounds.

CONCLUSION

Based on the current record, we find the information presented in the Petition, Preliminary Response, and accompanying evidence has demonstrated a reasonable likelihood that at least claims 1 and 16–24 of the '253 patent would have been obvious over Wyse and HPE. Under *SAS*, we

institute an *inter partes* review of all claims challenged under all grounds in the Petition. *See also PGS Geophysical AS*, 891 F.3d at 1360 (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”).

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon completion of the record.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–29 of the ’253 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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