Trials@uspto.gov
571-272-7822

Paper 57
Date: August 21, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

NALOX-1 PHARMACEUTICALS, LLC,
Petitioner,

v.

ADAPT PHARMA OPERATIONS LIMITED, and
OPIANT PHARMACEUTICALS, INC.,
Patent Owner.

---

IPR2019-00685
Patent 9,211,253 B2

---

Before ERICA A. FRANKLIN, ZHENYU YANG, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

# JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
*35 U.S.C. § 318(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 No. 9,211,253 B2 ("the '253 patent," Ex. 1001). We instituted trial to review the challenged claims. Paper 11 ("Dec."). Thereafter, Adapt Pharma Operations Limited and Opiant Pharmaceuticals, Inc. (collectively, "Patent Owner") filed a Response to the Petition (Paper 34, "PO Resp."), Petitioner filed a Reply (Paper 39), and Patent Owner filed a Sur-Reply (Paper 49). Petitioner also filed a Motion for Observations (Paper 51). An oral hearing for this proceeding was held on May 19, 2020, and a transcript of that hearing is of record. *See* Paper 53 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, and based on the evidence and argument presented in this proceeding, we conclude Petitioner has not established by a preponderance of the evidence that claims 1–29 of the '253 patent are unpatentable.

### *Related Proceedings*

Petitioner filed IPR2019-00686 and IPR2019-00687, challenging the same claims of the '253 patent with additional prior art. We denied those petitions. IPR2019-00686, Paper 11; IPR2019-00687, Paper 11.

The '253 patent is one of the 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 other patents listed in the Orange Book. Pet. 6; Paper 5, 1–2. We denied some of those petitions but instituted reviews in IPR2019-00688 (challenging U.S.

Patent No. 9,468,747) and IPR2019-00694 (challenging U.S. Patent No. 9,629,965). IPR2019-00688, Paper 11; IPR2019-00694, Paper 10. Concurrently with this Decision, we issue a final written decision in each of those cases.

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.) ("the Perrigo Case"). Pet. 5; Paper 5, 2. Petitioner is not involved in those actions. Pet. 5–6.

According to Patent Owner, on March 2, 2020, the Perrigo Case was dismissed with prejudice pursuant to a consent judgment. Paper 56, 3. On June 26, 2020, the district court entered final judgment in the Teva Case, holding invalid certain claims of four patents listed in the Orange Book under NARCAN. *Id.* at 3–4. Patent Owner states that its appeal from that judgment was docketed on August 3, 2020. *Id.* at 4.

*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.[2]

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. *Id.* at 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 prevent, recognize and respond to an overdose."). It points out, however, that some studies "reported that the nasal administration of naloxone is as effective as the intravenous route in opiate addicts," yet 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:

---

[1] Physicians' Desk Reference 2003, entry for NARCAN (Naloxone Hydrochloride Injection, USP).
[2] Where applicable, we cite to the original page numbers of the exhibits, and not the pagination added by the parties.

> 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 Claims*

Among the challenged claims, claims 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.

*Instituted Grounds of Unpatentability*

We instituted trial to determine whether claims 1–29 of the '253 patent are unpatentable based on the following grounds:

| Claims Challenged | 35 U.S.C. § | References |
|---|---|---|
| 1–3, 16–24, 28, 29 | 103 | Wyse,[3] HPE[4] |
| 4–7, 10–15, 25–27 | 103 | Wyse, Djupesland,[5] HPE |
| 8, 9 | 103 | Wyse, Djupesland, HPE, the '291 patent[6] |

Dec. 6.

Petitioner relies on the Declarations of Maureen D. Donovan, Ph.D. (Exs. 1002, 1201) and Günther Hochhaus, Ph.D. (Exs. 1003, 1202). Patent Owner relies on the Declarations of Stuart A. Jones, Ph.D. (Exs. 2201, 2300), Kenneth Williams, M.D. (Ex. 2202), Thomas Begres (Ex. 2203), Eric Karas (Ex. 2204), Robert L. Vigil, Ph.D. (Ex. 2205), and Declan Brides (Ex. 2207). Exhibits 2201, 2205, and 2207 were filed under seal, and Patent Owner has provided Exhibits 2208 and 2206 as the redacted version of Exhibits 2201 and 2205, respectively.

---

[3] Wyse et al., U.S. Patent No. 9,192,570 B2, issued November 24, 2015 (Ex. 1007).
[4] 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).
[5] Djupesland, Nasal Drug Delivery Device: Characteristics and Performance in a Clinical Perspective - A Review, 3 DRUG DELIV. & TRANSL. RES. 42–62 (2013) (Ex. 1010).
[6] Wermeling, U.S. Patent No. 8,198,291 B2, issued June 12, 2012 (Ex. 1015).

## ANALYSIS

### *Principles of Law*

To prevail in this *inter partes* review, 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 said 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); *KSR*, 550 U.S. at 406.

A party that asserts obviousness of a claim must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). "There is no suggestion to combine, however, if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999).

We analyze the instituted grounds of unpatentability in accordance with these principles.

*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.*

Petitioner asserts that:

> The POSA team would also include drug development professionals ["Pharmacologist POSA"] with 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.

In our Institution Decision, we adopted Petitioner's definition of the level of ordinary skill, which was undisputed at the time, because it was consistent with the level of skill reflected in the prior art of record and the disclosure of the '253 patent. Dec. 9; *see Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Patent Owner does not contest the level of skill as adopted in our Institution Decision, and we continue to apply that same skill level in our analysis for this Final Written Decision.

*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);[7] *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. 22–24. 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.*,

[7] *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)).

868 F.3d 1013, 1017 (Fed. Cir. 2017) (stating that claim terms need only be construed to the extent necessary to resolve the controversy).

*Prior-Art Disclosures*

Wyse

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.

Wyse discloses the results of preliminary formulation screening studies for 13 naloxone formulations, each including 20 mg/ml naloxone HCl and a different combination of excipients. *Id.* at 26:26–29, Table 13. Wyse reports that the study "surprisingly showed" that, in four of the five formulations that include benzalkonium chloride ("BAC")[8] as the preservative, the use of BAC "resulted in an additional degradant." *Id.* at 27:29–32, Table 13. According to Wyse, apart from the preservative, i.e., BAC, "Formulation 7," one of the BAC-containing formulations that unexpectedly resulted in degradant, "was believed to be ideal for nasal delivery." *Id.* at 27:32–34.

HPE

HPE lists pharmaceutical excipients, including BAC, benzyl alcohol, and disodium edetate ("EDTA"). Ex. 1012. HPE describes various information about each excipient, such as the applications in pharmaceutical formulation as well as safety. *Id.*

[8] Benzalkonium chloride is abbreviated as BAC in the Petition, and BZK in the Patent Owner Response.

For BAC, HPE teaches that in nasal formulations, it is used in "a concentration of 0.002–0.02% w/v." *Id.* at 56. HPE notes that BAC is "[i]ncluded in the FDA Inactive Ingredients Database" for nasal preparations. *Id.* at 57 (citation omitted).

Djupesland

Djupesland teaches that the Pfeiffer/Aptar single-dose intranasal delivery device has been used to administer certain intranasal migraine medications. Ex. 1010, 49. According to Djupesland, to use the device, which "consist[s] of a vial, a piston, and a swirl chamber," one holds it "between the second and the third fingers with the thumb on the actuator." *Id.* Djupesland explains that "[t]o emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications." *Id.*

The '291 Patent

The '291 patent "compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device." Ex. 1015, 7:61–63. The unit-dose delivery system employed is "Unitdose Second Generation," a commercially available disposable intranasal applicator from Pfeiffer. *Id.* at 8:12–16. The '291 patent describes the composition and volume of the formulation sprayed. *Id.* at 7:63–67, 8:16–18.

*Obviousness over Wyse and HPE*

Petitioner argues that claims 1–3, 16–24, 28, and 29 would have been obvious over Wyse[9] and HPE. Pet. 28–45. After reviewing the entire record, we conclude Petitioner has not shown by a preponderance of the evidence that the combination of Wyse and HPE renders any of the challenged claims obvious.

Claim 1 recites "between about 0.005 mg and about 0.015 mg of a preservative," and "between about 0.1 mg and about 0.5 mg of a stabilizing agent." Each of dependent claims 2, 3, 28, and 29 specifies BAC as the preservative and EDTA as the stabilizing agent. In this Decision, the central question turns on whether, based on evidence of the record in this proceeding, an ordinarily skilled artisan would have understood Wyse and HPE to teach away from using BAC as a preservative, especially in combination with the stabilizing agent EDTA, in an intranasal naloxone formulation. Because it is dispositive regarding all the challenged claims, we focus our analysis on this issue only.

Regarding claim 1, Petitioner argues that Wyse teaches using an antimicrobial agent, which is a preservative, in an amount of 0.1% to 2% by weight of the formulation. Pet. 32 (citing Ex. 1007, 7:20–28). Because Wyse does not specify "the types of antimicrobial agents that may be used,"

---

[9] Wyse issued on November 24, 2015, from an application filed on December 19, 2014. Ex. 1007, codes (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.

Petitioner asserts a Formulator POSA would have consulted HPE to choose the antimicrobial agents in appropriate amounts based on their potencies. *Id.* (citing Ex. 1002 ¶ 134).

According to Petitioner, "Wyse discloses using quantities of preservative between 0.1% w/v and 2% w/v" based on benzyl alcohol, the preservative exemplified in Wyse. *Id.* at 33. Petitioner argues that benzyl alcohol "is usually used at concentrations such as 5 mg/mL (0.5% w/v) because it is only moderately active against Gram-positive organisms and less active against Gram-negative bacteria." *Id.* (citing Ex. 1012, 64).

In contrast, Petitioner asserts, BAC "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 32 (citing Ex. 1002 ¶¶ 64, 137; Ex. 1012, 56). Thus, Petitioner concludes, "[a] POSA would have been particularly motivated to use benzalkonium chloride ('BAC') as a preservative in such a nasal spray," in the amount of 0.002–0.02 mg (at the concentration of 0.002–0.02% w/v in the volume of 100 μL), which fully encompasses the 0.005–0.015 mg range recited in challenged claim 1. *Id.* at 32–33 (citing Ex. 1002 ¶ 138; Ex. 1012, 56). In other words, as Patent Owner points out, Petitioner's "arguments for obviousness of the recited preservative amounts hinge on establishing that the POSA would have used [BAC]." PO Resp. 5.

In our Institution Decision, we agreed with Patent Owner that both Wyse and HPE taught away from using BAC as the preservative, especially in combination with the stabilizing agent EDTA, in formulating intranasal naloxone. Dec. 18–22. Although we focused on certain dependent claims when discussing the teaching-away issue at institution, after considering the

full record developed through trial, we agree with Patent Owner that the teaching-away argument applies to all challenged claims. We highlight relevant arguments and evidence in the following discussion.

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, *see also id.* at 28:23–27 ("Applicant found that, surprisingly, commonly used excipients including . . . benzylalkonium chloride, were found to increase degradation of naloxone.").

Petitioner acknowledges Wyse's disclosure on this issue (Pet. 55 (citing Ex. 1007, 27:30–34, 41–44)), but emphasizes that "[n]o other prior art cited by [Patent Owner] would have directed a POSA away from using BAC in an intranasal naloxone formulation." Reply 9–10. We are not persuaded by this argument.

As Petitioner acknowledges, an ordinarily skilled artisan "would have been concerned about naloxone degradation," and would have "been motivated to choose ingredients to render the formulation chemically and microbiologically stable." Pet. 19; *see also id.* ("Ideally, nearly all of the naloxone active ingredient would remain present after storage; the solution would have resisted any changes in color or formation of particulate matter; and the solution would have been free of microbial growth or ingress." (citing Ex. 1002 ¶ 50)).

In this proceeding, Wyse is the only reference of record that compares naloxone formulations having different excipient combinations, and provides stability data for intranasal naloxone formulations. Thus, we find that, contrary to Petitioner's assertion that "a POSA would not have granted [Wyse's] statements much merit" (Pet. 55), an ordinarily skilled artisan, when "determin[ing] what antimicrobial agents he or she should consider in developing a nasal formulation of naloxone" (*id.* at 33), would have taken into consideration, and indeed, would have given significant weight, to the only naloxone formulation stability data disclosed in Wyse.

Petitioner contends that ordinarily skilled artisans "reading the disclosure of Wyse have concluded that it does not teach away" from using BAC. Pet. 55. As support, Petitioner cites Glende,[10] "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, 76). Glende, however, reached this conclusion after also reviewing the WIPO publication equivalent of the challenged '253 patent (Ex. 1031, 54), which disclosed BAC-containing formulations were "storage-stable" (*id.* at 54, 64). Thus, we agree with Patent Owner that "Glende's conclusion was based on knowledge of the patented invention which disclosed the stability of the patentee's

[10] 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).

formulations, not what the POSA would have understood from the prior art." *See* PO Resp. 12.

Regarding the teachings of Wyse, Petitioner argues that an ordinarily skilled artisan "would not have properly concluded that Wyse taught away from using BAC with naloxone." Pet. 54–55. According to Petitioner, because "Wyse performed degradation testing on multiple different formulations combining multiple different excipients, it cannot be conclusively determined that any individual excipient was responsible for any instability issues in the disclosed formulation." *Id.* at 55; *see also* Reply 6 ("Wyse discloses that his prototyping studies, in which *combinations* of excipients were tested together, would not permit a conclusion that *any one ingredient* in the combinations was responsible for naloxone degradation."). We are not persuaded by this argument either.

In its screening tests, Wyse tested benzyl alcohol, paraben, and BAC preservatives. Ex. 1007, Table 13. Of special note is that formulations 13 and 13A contain benzyl alcohol as the preservative, whereas formulations 14 and 14A contain BAC as the preservative. *Id.*, Table 13. Wyse observed an additional degradant in formulations 14 and 14A (*id.* at 27:29–32) even though, but for the preservative, formulation 14 is identical to formulation 13, and formulation 14A is identical to formulation 13A (*id.*, Table 13). Based on these results, Wyse concluded that "benzyl alcohol and paraben preservatives were acceptable, but benzalkonium chloride [BAC] was not, due to increased observed degradation." *Id.* at 27:42–44. On this record, Petitioner has not shown this conclusion was unreasonable, or that an ordinarily skilled artisan, based on knowledge possessed at the time of the invention, would have otherwise doubted Wyse's express teaching that BAC

was not an acceptable preservative because it caused the increased degradation that Wyse observed in its tests.

Petitioner also questions whether, in Wyse, BAC "specifically resulted in additional naloxone degradation, rather than degradation of another component." Pet. 55. We disagree. Wyse specified that BAC increases "degradation of naloxone." *Id.* at 28:23–27, *see also id.* at 26:32–34 (explaining "Naloxone RP-HPLC assay for purity"), 27:19–21 (discussing the "stability of naloxone HCl" and "degradation of naloxone HCl").

Petitioner further argues that "*if* the 'additional degradant' was a naloxone degradant, it would likely be an oxidation degradant." Reply 5. According to Petitioner, "a POSA would have known that BAC could *not* have been responsible for the production of any oxidative degradants." *Id.* The evidence of the record does not support Petitioner's position.

Petitioner relies on the Donovan Declaration to support its argument that the additional degradant reported by Wyse "would *likely* be an oxidation degradant."[11] Reply 5 (citing Ex. 1201 ¶¶ 13, 15, emphasis added). Dr. Donovan's testimony on this point, however, is much more tentative:

---

[11] Petitioner also asserts that "the 'additional degradant' in these formulations was identified in a separate document as Impurity E—*i.e.*, 2,2'-binaloxone—the primary oxidation degradation product of naloxone." Reply 5. As support, Petitioner relies on Exhibit 2188, "Indivior NDA Module 3.2.P.2." *Id.* (citing Ex. 2188); Paper 48, 23. Exhibit 2188, however, is a third-party confidential document that is not alleged to be in the prior art and was, and remains, under seal. Paper 32, 3. Thus, Petitioner has not shown that an ordinarily skilled artisan, at the priority date of the claimed invention, would have understood that the "additional degradant" in Wyse is Impurity E.

> I think a person of ordinary skill in the art *would hold open the possibility* that it was an oxidative degradant because that's what Wyse was trying to accomplish, but they wouldn't have any reason to believe it was a particular form of an -- of the oxidative degradants known or unknown and, yes, they, again, couldn't anticipate what that material was without additional information but certainly oxidative degradants would be in keeping with what *a POSA would postulate might show up* in these mixtures.

Ex. 2215, 502:14–503:2 (emphases added). In view of such equivocal testimony, we are not persuaded by Petitioner's argument that an ordinarily skilled artisan would have attributed the "additional degradant" disclosed in Wyse to oxidative degradation, and thus would have subsequently deduced that BAC could not have caused such degradation.

Petitioner argues that "the evidence does not show that BAC is *incompatible* with naloxone, and thus does not teach away from its inclusion in a naloxone formulation." Pet. 55. According to Petitioner, "[a] POSA would have known that in order to conclude that BAC and naloxone were incompatible, one would need to study the individual combination of the two compounds." Reply 7, *see also id.* ("To determine the root cause of any problems, a POSA would have to evaluate each excipient and experimental condition individually and potentially evaluate other factors."). Petitioner overstates the standard for evaluating whether a reference teaches away.

A reference teaches 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." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Wyse explicitly and unambiguously discourages the use of BAC in intranasal naloxone formulations. Wyse found BAC "increase[d] degradation of naloxone" (Ex. 1007, 28:26–27), and excluded BAC from the naloxone formulations chosen for further study (*id.* at 28:41–47, Table 14).

As explained above, on the record presented in this proceeding, we are not persuaded by Petitioner's arguments that an ordinarily skilled artisan would have interpreted Wyse's teachings differently.

Accordingly, Wyse teaches away from using BAC as the preservative because it directly "criticize[s], discredit[s], or otherwise discourage[s] the solution claimed." *See In re Fulton*, 391 F.3d at 1201. This is so despite the fact that, as Petitioner emphasizes, one of the five BAC-including formulations tested by Wyse did not result in additional degradants. Pet. 55. After all, a reference teaches 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" in the challenged claim. *Gurley*, 27 F.3d at 553.

Here, Wyse does both. It not only presents results showing that BAC is not acceptable for use in intranasal naloxone formulations, but also provides data demonstrating that other preservatives, such as benzyl alcohol, are stable in such formulations. *Id.* at 27:41–44, 28:41–29:27. Indeed, Wyse teaches that the BAC-containing version of an otherwise "ideal" naloxone nasal formulation produced an additional degradant, whereas the benzyl alcohol-containing version of that formulation was stable. *Id.* at 27:29–37, Tables 14, 15. Wyse ultimately determined that two formulations using benzyl alcohol, and excluding BAC, as the preservative were stable and warranted further development. *Id.* at 29:19–21, Table 15.

We recognize the general teaching of prior art, including HPE, that BAC is an antimicrobial preservative that may be used in, and is FDA approved for, nasal formulations. Pet. 32–33, 35–36; Reply 11; *see also* Ex. 1012, 56–57 (showing BAC is in the FDA's inactive ingredients

database for nasal preparations). This, however, is insufficient to defeat Wyse's teaching away. As explained above, in this proceeding, Wyse is the only prior-art reference of record that specifically addresses the effect of BAC on the stability of intranasal naloxone formulations. Thus, even if an ordinarily skilled artisan might have generally contemplated including BAC because it was a preservative known for use in nasal formulations, such an artisan would have been dissuaded from doing so because Wyse expressly teaches that BAC is unacceptable for use in intranasal naloxone formulations.

In sum, based on the evidence and arguments presented in this proceeding, we find Wyse teaches away from using BAC in intranasal naloxone formulations. Although claim 1 does not require BAC as the preservative, it recites a specific range, "between about 0.005 mg and about 0.015 mg," for the amount of the preservative. To account for this limitation, Petitioner solely relies on the potency and the commonly used concentrations of BAC. Pet. 32–33; *see also* Tr. 18:9-22 (Petitioner acknowledging that "all of our argument has been tailored to the obviousness of using BAC" and that it has not presented additional arguments or evidence for those claims not expressly limited to BAC). As a result, we conclude that Petitioner has not shown by a preponderance of the evidence that all claims challenged under this ground would have been obvious over Wyse and HPE.

In addition, each of dependent claims 2, 3, 28, and 29 recites BAC as the preservative and EDTA as the stabilizing agent. HPE specifically teaches that "[n]asal formulations containing benzalkonium chloride [BAC] and disodium edetate [EDTA], 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 BAC and EDTA are "known to be local irritants," and that using them together with would "produce an inflammatory reaction" would have discouraged an ordinary artisan from doing so. *See* PO Resp. 14; Dec. 21–22. As a result, we find HPE further teaches away from using BAC together with EDTA in intranasal formulations. For this additional reason, we conclude that Petitioner has not shown by a preponderance of the evidence that claims 2, 3, 28, and 29 would have been obvious over Wyse and HPE.

*Other Grounds*

Petitioner argues that claims 4–7, 10–15, and 25–27 would have been obvious over Wyse, Djupesland, and HPE, and claims 8 and 9 would have been obvious over Wyse, Djupesland, HPE, and the '291 patent. Pet. 45–54. Each of these claims depends, directly or indirectly, from claim 2, which requires the combination of BAC and EDTA.

Petitioner relies on Djupesland and the '291 patent for teaching the additional limitations in the claims challenged under these two grounds, but relies only on the same teachings of Wyse and HPE as discussed above for the limitation they incorporate by dependency from claim 2. *Id.* As explained above, Wyse teaches away from using BAC in intranasal naloxone formulations, and HPE teaches away from using BAC together with EDTA in such formulations. Thus, we conclude that Petitioner has not shown by a

preponderance of the evidence that the claims challenged under these two grounds would have been obvious as asserted in the Petition.

## CONCLUSION

Petitioner has not demonstrated by a preponderance of the evidence that claims 1–29 of the '253 patent would have been obvious based on the challenges presented in the Petition.

In summary:

| Claims | 35 U.S.C. § | References | Claims Shown Unpatentable | Claims Not shown Unpatentable |
|---|---|---|---|---|
| 1–3, 16–24, 28, 29 | 103 | Wyse, HPE | | 1–3, 16–24, 28, 29 |
| 4–7, 10–15, 25–27 | 103 | Wyse, Djupesland, HPE | | 4–7, 10–15, 25–27 |
| 8, 9 | 103 | Wyse, Djupesland, HPE, the '291 patent | | 8, 9 |
| **Overall Outcome** | | | | 1–29 |

## ORDER

Accordingly, it is

ORDERED that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–29 of the '253 patent are unpatentable; and

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

For PETITIONER:

Yelee Kim
Richard Berman
Christopher Yaen
Janine Carlan
Bradford Frese
ARENT FOX
Yelee.kim@arentfox.com
Richard.berman@arentfox.com
Christopher.yaen@arentfox.com
Janine.carlan@arentfox.com
Bradford.frese@arentfox.com

For PATENT OWNER:

Jessica Mackay
Ann Kotze
GREEN GRIFFITH & BORG-BREEN, LLP
jmackay@greengriffith.com
akotze@greengriffith.com

Jessamyn Berniker
David Krinsky
Anthony Sheh
WILLIAMS AND CONNOLLY LLP
jberniker@wc.com
dkrinsky@wc.com
asheh@wc.com