

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMPHASTAR PHARMACEUTICALS, INC.,
Petitioner,

v.

AEGIS THERAPEUTICS, LLC,
Patent Owner.

IPR2021-01324
Patent 10,682,414 B2

Before ROBERT A. POLLOCK, TIMOTHY G. MAJORS, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

HARDMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner Amphastar Pharmaceuticals, Inc. requests *inter partes* review of claims 1–20 of U.S. Patent No. 10,682,414 B2 (“the ’414 patent,” Ex. 1001). Paper 1 (“Pet.”). Patent Owner Aegis Therapeutics, LLC filed a Preliminary Response, and the parties filed authorized supplemental briefing regarding discretionary denial under 35 U.S.C. § 325(d). Paper 7 (“Prelim. Resp.”); Papers 9–11.

Taking into account the arguments in the Preliminary Response and supplemental briefing, we determine that the Petition demonstrates “a reasonable likelihood that petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Thus, we institute an *inter partes* review.

The following preliminary findings of fact and conclusions of law are made solely for determining whether to institute review. Any final decision will be based on the full trial record.

A. *Real Parties in Interest*

Petitioner identifies itself as the real party in interest (“RPI”). Pet. 1. Patent Owner identifies itself and ARS Pharmaceuticals, Inc. as RPIs. Paper 5, 1.

B. *Related Matters*

Petitioner represents that it is unaware of any judicial or administrative matters, reexamination certificates, or pending prosecution concerning the ’414 patent. Pet. 1. Petitioner identifies U.S. Patent Application No. 16/869,461 (filed May 7, 2020) as related to the ’414 patent. *Id.*

Patent Owner identifies no related matters. Paper 5 (Patent Owner Mandatory Notices), 1.

C. The '414 Patent (Ex. 1001)

The '414 patent, titled “Intranasal Epinephrine Formulations and Methods for the Treatment of Disease,” relates to intranasal epinephrine formulations and methods of treating anaphylaxis.¹ Ex. 1001, code (54), 1:17–19. Per the Specification, “[a]naphylaxis is a severe, potentially life-threatening type-1 hypersensitivity reaction (systemic allergic reaction) that affects many body systems.” *Id.* at 1:38–40. The Specification notes that although epinephrine injection is the standard treatment for anaphylaxis, there have been “numerous reports of the highly variable exposures from injection products depending on the location of the injection (intramuscular or subcutaneous), and other factors such as body mass index (BMI).” *Id.* at 1:60–2:9. The Specification identifies a “need for alternative, needle-free and non-invasive methods for dosing epinephrine.” *Id.* at 2:24–25.

Challenged claim 1 relates to a method of treating a type-1 hypersensitivity reaction in a mammal via intranasal administration of an aqueous nasal spray pharmaceutical formulation that includes between about 0.1 mg and about 2.4 mg of epinephrine, or a salt thereof, as the anaphylaxis active ingredient. *Id.* at 72:15–23.

¹ The '414 patent claims priority to a provisional application filed December 21, 2018. Ex. 1001, code (60). Petitioner assumes, and Patent Owner does not dispute, that the challenged claims are entitled to claim priority to this date. Pet. 8–9; *see generally* Prelim. Resp. We similarly assume that the challenged claims are entitled to claim priority to December 21, 2018.

The Specification includes exemplary formulations (*id.* at 60:63–62:21, Tables 2–4) and two clinical studies (*id.* at 63:30–71:58). The first clinical study assesses the comparative bioavailability of epinephrine after intranasal administration and intramuscular administration. *Id.* at 63:30–39. The intranasal formulation comprised 0.3 mg epinephrine, dodecylmaltoside (“DDM”²), benzalkonium chloride (“BKC”), and ethylenediaminetetraacetic acid (“EDTA”). *Id.* at 64:26–31. The intramuscular injection delivered 0.3 mg of epinephrine. *Id.* at 64:31–33. The Specification reports that “[m]ean plasma concentration of epinephrine from IN [intranasal] administration remained significantly below that of epinephrine from intramuscular epinephrine.” *Id.* at 66:15–18; *see also id.* at Fig. 3.

The second clinical study first assesses “the optimal dose of a formulation of intranasal epinephrine,” then compares the bioavailability of that optimal intranasal dose to an intramuscular dose. *Id.* at 66:49–57. Subjects first received escalating intranasal doses of 0.5 mg, 1.0 mg, and 2.0 mg epinephrine, where the formulations again comprised epinephrine, DDM, BKC, and EDTA. *Id.* at 66:62–67:33. The 1.0 mg and 2.0 mg intranasal formulations exhibited a lower T_{\max} than the intramuscular formulation exhibited in the first clinical study, and the area under the plasma concentration time curve (“AUC”) was higher for all intranasal formulations than for the intramuscular formulation. *Id.* at 69:39–58, Figs. 4–7.

² DDM, an alkylglycoside (or alkylsaccharide), functions as an absorption enhancer, and is sold under the tradename INTRAVAIL. Ex. 1001, 35:50–36:14, 46:67–47:11. The INTRAVAIL tradename covers a class of alkylsaccharides. Ex. 1017, 6–7.

The bioavailability of the 1.0 mg intranasal epinephrine dose was then compared to that of a 0.3 mg epinephrine intramuscular injection. *Id.* at 66:62–67:17. According to the Specification, “the plasma time vs. concentration curve for 1.0 mg IN epinephrine is very similar to that for 0.3 mg IM epinephrine (EpiPen®) administered in the thigh.” *Id.* at 69:66–70:42, Figs. 8, 9. Per the Specification, these data “demonstrate that 1.0 mg intranasal epinephrine can be formulated to be highly similar to or better than a 0.3 mg intramuscular injection of epinephrine.” *Id.* at 45–48.

D. The Challenged Claims

Independent claim 1, the only challenged independent claim, is reproduced below:

1. A method of treatment of a type-1 hypersensitivity reaction in a mammal comprising administering intranasally to the mammal in need thereof an aqueous nasal spray pharmaceutical formulation; wherein the aqueous nasal spray pharmaceutical formulation comprises:
 - an anaphylaxis active ingredient, wherein the anaphylaxis active ingredient consists of between about 0.1 mg and about 2.4 mg of epinephrine, or a salt thereof in a single dose.

Ex. 1001, 72:15–23. The challenged dependent claims add additional features. For example, claim 3 depends from claim 1 and requires that the intranasal administration of the claimed nasal spray “provides a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis.” *Id.* at 72:33–37. Claim 7 depends from claim 1 and requires, among other things, that the claimed nasal spray comprises “one or more absorption enhancement agents.” *Id.* at 72:54–62. Claim 11 depends from claim 7 and requires that BKC is present in specific amounts, as the sole absorption enhancement agent or with one or more other absorption

enhancement agents. *Id.* at 73:31–43. Claims 19 and 20 depend (directly or indirectly) from claim 3, and require that the nasal spray comprises, among other things, DDM and BKC. *Id.* at 74:23–45.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–20 are unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–18	§ 102	Potta ³
1–20	§ 103	Potta, Maggio, ⁴ Munjal ⁵
1–20	§ 103	Srisawat, ⁶ Maggio, Munjal

Pet. 4. Petitioner support its contentions with the Declarations of Hugh D. C. Smyth, Ph.D. and Steven F. Weinstein, M.D. Exs. 1002, 1003.

³ Potta et al., U.S. Patent Pub. 2018/0289617 A1, published October 11, 2018 (“Potta,” Ex. 1004).

⁴ Maggio, U.S. Patent Pub. 2014/0107145 A1, published April 17, 2014 (“Maggio,” Ex. 1005). The parties sometimes refer to this reference as “Maggio ’145.”

⁵ C. Srisawat et al., *A Preliminary Study of Intranasal Epinephrine Administration as a Potential Route for Anaphylaxis Treatment*, 34 ASIAN PAC. J. ALLERGY. IMMUNOL. 38 (2016) (“Srisawat,” Ex. 1006).

⁶ S. Munjal et al., *A Randomized Trial Comparing the Pharmacokinetics, Safety, and Tolerability of DFN-02, an Intranasal Sumatriptan Spray Containing a Permeation Enhancer, with Intranasal and Subcutaneous Sumatriptan in Healthy Adults*, 56 HEADACHE 1455 (2016) (“Munjal,” Ex. 1020).

II. ANALYSIS

A. Discretionary Denial Under § 325(d)

The parties dispute whether the Board should discretionarily deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 15–16; Pet. 62–64; Papers 10, 11.

1. Standard for Exercising Discretion Under Section 325(d)

Section 325(d) provides that the Director⁷ may “reject the petition” if “the same or substantially the same prior art or arguments previously were presented to the Office.” The Board analyzes this issue under a two-part framework:

(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential).

2. Whether the Same or Substantially the Same Art or Arguments Were Previously Presented to the Office

We find that three of Petitioner’s four asserted references were before the Office during prosecution of the application that led to the ’414 patent. First, there is no dispute that Potta is listed on an Information Disclosure Statement (“IDS”) that appears in the prosecution history. *See* Pet. 63; Prelim. Resp. 16–17. Second, although Maggio itself is not listed on an

⁷ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

IDS, there is no dispute that counterparts to Maggio are listed on an IDS. Pet. 63; Prelim. Resp. 28. Patent Owner demonstrates, and Petitioner does not dispute, that at least one of these counterparts is substantially identical to Maggio. Prelim. Resp. 28; *see generally* Paper 10. Third, there is no dispute that Srisawat is discussed in the Specification of the '414 patent. Pet. 64; Prelim. Resp. 36.

The parties agree that Petitioner's fourth reference (Munjal) was not before the Examiner. Pet. 64; Prelim. Resp. 31. Patent Owner argues that Petitioner relies on Munjal for disclosure relating to absorption enhancement agents⁸ (and DDM in particular), and thus it is cumulative of prior art the Examiner evaluated during prosecution, including Fleming (U.S. Patent Pub. 2015/0005356 A1, Ex. 1010), which discloses alkylglycosides as nasal permeation enhancers for the delivery of epinephrine, and Levitt (U.S. Patent Pub. 2010/0209357 A1), which discloses DDM. Prelim. Resp. 31–32; *see also* Pet. 12 (conceding that the Examiner relied on Levitt for disclosure of a pharmaceutical composition containing DDM as a surfactant to improve delivery). Taking into account the parties' arguments (including those in the supplemental briefing), for the reasons provided by Patent Owner, we agree that Munjal is cumulative of art considered by the Examiner. *See* Prelim. Resp. 31–32; Paper 11, 1–2.

Because the art in the Petition is the same or substantially the same as that previously presented to the Office, we move to part two of the *Advanced Bionics* analysis. *See Advanced Bionics*, Paper 6 at 10.

⁸ We use the terms “absorption enhancement agent,” “absorption enhancer,” “permeation enhancer,” “penetration enhancer,” and the like interchangeably. *See, e.g.*, Ex. 1002 ¶ 98; Ex. 1001, 34:57–64.

3. *Whether the Office Erred in a Manner Material to the Patentability of Challenged Claims*

We agree with Petitioner that the Office materially erred during prosecution, insofar as the Examiner misapprehended or overlooked relevant teachings of Potta. Critically, during prosecution, the applicant achieved allowance by amending claim 1 to limit the anaphylaxis active agent to epinephrine. *See* Pet. 12 (noting that claim 1 was amended to recite that the anaphylaxis active agent “*consists of* . . . epinephrine”). The applicant argued that this amendment distinguished the claims over Fleming, which discloses intranasal formulations comprising epinephrine *plus* a COMT (catechol-o-methyl transferase) inhibitor and/or a vasodilator. *Id.*; *see also* Prelim. Resp. 11. The Examiner agreed, stating in relevant part that the cited prior art did not teach or suggest a formulation limited to epinephrine as the only anaphylaxis active ingredient. Ex. 1007, 49; Pet. 13; Prelim. Resp. 11. The Examiner also stated that an “[a]dditional search found close art of intranasal spray comprising epinephrine and bronchodilator, ***but not epinephrine alone***, as anaphylaxis active ingredient.” Ex. 1007, 49 (emphasis added). Nevertheless, we find that there was Examiner error because, as will be discussed below (*see infra* Section II.D), Potta, which was before the Office, teaches intranasal sprays according to at least some challenged claims that comprise epinephrine as the only anaphylaxis active ingredient. Pet. 63; Paper 10, 3.

Patent Owner argues that the Examiner did not err because he “was well aware that Potta explicitly taught away from the lower claimed range of the ’414 patent for intranasal [epinephrine] administration.” Prelim. Resp. 26. This argument is unavailing, because Patent Owner does not point to

any contemporaneous evidence demonstrating that the Examiner had this view of Potta. *See Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989) (noting that attorney argument is “no substitute for evidence”).

The record here indicates material error. That is, the Examiner did not expressly address Potta and appears to have misapprehended or overlooked Potta’s specific teachings that impact patentability of the challenged claims. *Advanced Bionics*, 8–9 n.9, 10–11.

4. *Conclusion*

We determine that the Examiner materially erred in not recognizing that prior art of record in prosecution—in particular, Potta—teaches intranasal sprays according to at least some challenged claims that comprise epinephrine alone, which is subject matter the Examiner apparently believed was missing in the prior art. Because two of the three grounds are based on Potta and cover all of the challenged claims, we find that § 325(d) is not sufficiently implicated⁹ and we decline to exercise our discretion to deny review under Section 325(d).

B. *Level of Ordinary Skill in the Art*

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art (sometimes referred to herein as “POSA” or “skilled artisan”) as of the December 21, 2018 effective filing date of the challenged claims. Petitioner contends:

a person of ordinary skill in the art (POSA) would have been composed of an individual or a team that would have included (1) an advanced degree (e.g., M.D., Pharm. D., Ph.D., or D.V.M.) and training in pharmacology, pharmaceutical sciences

⁹ *See SAS Q&As*, D1 (June 5, 2018) (available at https://www.uspto.gov/sites/default/files/documents/sas_qas_20180605.pdf).

or related discipline or experience treating type-1 hypersensitivity reactions in a mammal and (2) at least two years of experience with the development of small molecule pharmaceutical formulations and the development and science of intranasal or mucosal delivery systems or the treatment of type-1 hypersensitivity reactions in a mammal.

Alternatively, the POSA would have been composed of an individual or a team that would have included (1) a bachelor's degree or similar; and (2) more than seven years of experience with the development of small molecule pharmaceutical formulations and the development and science of intranasal or mucosal delivery systems or the treatment of type-1 hypersensitivity reactions in a mammal.

To the extent necessary, a POSA may collaborate with one or more other POSAs, such as an expert in pharmaceutical formulations or a medical doctor, for one or more aspects with which the other POSA may have expertise, experience, and/or knowledge.

Pet. 7–8 (spacing added). For purposes of the Preliminary Response, Patent Owner applies Petitioner's proposal. Prelim. Resp. 14.

Because Petitioner's proposed level of ordinary skill in the art is consistent with the cited prior art and is undisputed on this record, we adopt it for purposes of this Decision.

C. Claim Construction

We interpret a claim “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).” 37 C.F.R. § 42.100(b). Under this standard, we construe 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.” *Id.*

Petitioner addresses two terms, which we analyze below. Patent Owner “does not offer any claim constructions” at this stage. Prelim. Resp. 13. Any final written decision entered in this case may include final claim constructions that differ from the preliminary understanding of the claims set forth below, or from any discussion of claim scope provided in our analysis below. Any final claim constructions will be based on the full trial record.

1. “*A method of treatment*” (*Independent Claim 1*)

Petitioner contends that the portion of claim 1’s preamble reciting “[a] method of treatment” should be construed as non-limiting, because it merely states the purpose or intended use of the formulations recited in the claim, but offers no additional step, limitation, or antecedent basis for the claim.¹⁰ Pet. 13–14.

“[A]s a general rule preamble language is not treated as limiting.” *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1327 (Fed. Cir. 2019) (citations omitted). Exceptions arise where, for example, the preamble (1) “recites essential structure or steps”; (2) provides antecedent basis for terms in the claim body; or (3) was relied on during prosecution to distinguish the claimed invention from prior art. *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). “[A] preamble is not limiting ‘where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use

¹⁰ In the event we find this preamble phrase limiting, Petitioner alternatively proposes a construction for the phrase. Pet. 14. Because, on this record, we agree with Petitioner that this phrase is not limiting, we do not address Petitioner’s proposed construction.

for the invention.” *Id.* (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

We agree with Patent Owner that Petitioner appears to be addressing whether the phrase “[a] method of treatment” is limiting in the sense that claim 1 requires actual treatment, e.g., some measure of efficacy in treating a type-1 hypersensitivity reaction in a mammal in need thereof. *See* Prelim. Resp. 13 (characterizing Petitioner’s proposed constructions as “focus[ing] on whether the claims include an ‘efficacy’ requirement and/or how ‘efficacy’ should be defined”). We preliminarily determine that this phrase does not invoke an efficacy requirement.¹¹

On this record nothing persuades us that this portion of the preamble falls outside the general rule that preamble language is not limiting. The phrase “[a] method of treatment” does not recite an essential structure or step that “result[s] in a manipulative difference in the steps of the claim.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). Rather, the body of claim 1 recites (in general terms) intranasal administration of a particular nasal spray in particular amounts to a subset of mammals. *Id.* at 1375. This method is “performed in the same way regardless [of] whether or not the patient experiences” an efficacious result. *Id.* Second, “[a] method of treatment” does not provide antecedent

¹¹ Although we preliminarily find that the phrase “[a] method of treatment” does not invoke an efficacy requirement, this does not mean that the preamble has no limiting effect whatsoever. For example, we recognize that “[a] method of treatment of a type-1 hypersensitivity reaction in a mammal . . . in need thereof” defines the intended patient population. *See, e.g., TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1323–24 (Fed. Cir. 2015) (parsing preamble).

basis for terms in the claim body. *See Arctic Cat Inc.*, 919 F.3d at 1329. Finally, nothing on this record indicates that the Examiner or applicant relied on this phrase during prosecution to distinguish prior art. *See id.*

Accordingly, for purposes of this Decision, we find that the portion of claim 1’s preamble reciting “[a] method of treatment” merely states the intended use or purpose of the claimed method, and therefore does not limit the scope of claim 1.

2. “*provides a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis*” (Dependent Claim 3)

Claim 3 recites:

The method of claim 1, wherein:
intranasal administration of the single dose of the aqueous nasal spray pharmaceutical formulation to the mammal ***provides a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis.***

Ex. 1001, 72:33–37 (emphasis added). Petitioner argues that the bolded phrase (“***provides a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis***”) is not limiting because it is a “[c]oncluding statement[] of intended result[]” that “do[es] not result in ‘a manipulative difference in the steps of the claim.’” Pet. 17 (quoting *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018) (quoting *Bristol-Myers Squibb Co.*, 246 F.3d at 1376)).

On this record, we disagree with Petitioner that claim 3 does not result in a manipulative difference in the steps of the claim. Stated differently, claim 3 appears to permit some manipulative differences in the steps of the claim. For example, claim 3, by virtue of its dependency from claim 1, recites a range of doses (about 0.1 mg to about 2.4 mg), and Petitioner has

not established that all of the claimed doses would provide a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis in all claimed mammals. Petitioner contends that the Specification “confirms that the claimed dosage contains a ‘therapeutically effective amount’ of epinephrine,” but fails to specifically cite any particular portion of the Specification to support this contention. *See* Pet. 17–18 (merely citing “*Supra.*”¹²); *cf. Bristol-Myers Squibb*, 246 F.3d at 1375 (finding that the specification described the claimed dosages as “antineoplastically effective”). Claim 3 also embraces a variety of aqueous nasal spray pharmaceutical formulations. The record reflects that the composition of the intranasal formulation could affect the absorption of epinephrine. *See, e.g.*, Ex. 1006, 4 (“Another issue that could affect IN [intranasal] absorption is the nasal spray formulation.”); Ex. 1002 ¶ 146; Ex. 1003 ¶ 419. Thus, claim 3 permits manipulation of the epinephrine dose and formulation to achieve the recited result, and on this record Petitioner has not established that despite such manipulations, the claimed method would nevertheless result in a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis.

This conclusion is supported by the doctrine of claim differentiation. *See Bristol-Meyers Squibb*, 246 F.3d at 1376 (noting that the doctrine creates

¹² To the extent Petitioner’s use of “[s]upra” is intended to point to the previous citation, the previously-cited material, i.e., Ex. 1002 ¶¶ 64–65 and Ex. 1003 ¶¶ 64–65, also does not point to any portion of the Specification that specifically ties the claimed dosage range and formulations to either therapeutically effective amounts of epinephrine, or to plasma epinephrine concentrations that are efficacious for the treatment of anaphylaxis, in the claimed mammals.

a presumption that each claim in a patent has a different scope). Petitioner recognizes that “the intended plasma epinephrine concentration efficacious for the treatment of anaphylaxis of claim 3 is the distinction between claim 1 and claim 3.” Pet. 18. Petitioner argues, however, that claim differentiation is not a “hard and fast rule of construction,” and “cannot save a non-limitation.” *Id.* (quoting *Bristol-Meyers Squibb*, 246 F.3d at 1376; citing *Copaxone*, 906 F.3d at 1023). But unlike the claims in *Bristol-Meyers Squibb* and *Copaxone*, claim 3 here does appear to permit a manipulative difference in the claimed steps, and thus “limit[s] the options covered by the subject matter” of claim 1 “to options that produce the concretely specified results.” *L’Oréal USA, Inc. v. Olaplex, Inc.*, 844 F. App’x 308, 324 (Fed. Cir. 2021).

Because we find the subject phrase of claim 3 limiting, we proceed to address Petitioner’s alternative proposed construction. Specifically, Petitioner argues that if the phrase is limiting, the word “efficacious” within this phrase should be construed as

elicits a biological or medicinal response in a tissue, system, or individual that is being sought by a researcher, healthcare provider or individual, which may, but need not necessarily, eliminate one, more, or all symptoms of anaphylaxis and may also prevent progression of anaphylaxis or the appearance of further symptoms.

Pet. 19. Although the Specification does not explicitly define “efficacious,” Petitioner bases its construction on the Specification’s express definition of “therapeutically effective amount,” and on the “broad use of efficacy” in the Specification and claims. *Id.* at 19–20.

On this record, we agree with Petitioner that the Specification's broad definition of "therapeutically effective amount" informs the construction of the word "efficacious" as recited in claim 3. *See, e.g.*, Pet. 15, 19. The Specification defines "therapeutically effective amount" (or "therapeutically effective dose") as an

amount or dose of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, or individual that is being sought by a researcher, healthcare provider or individual. A therapeutically effective amount may, but need not necessarily, eliminate one, more, or all symptoms of a disease, disorder, or condition being treated. A therapeutically effective amount may also prevent disease progression or the appearance of further symptoms.

Ex. 1001, 40:61–41:3. We note, however, that this definition informs, in the context of the '414 patent, what it means to be "effective" (or "efficacious") in treating a disease, disorder, or condition generally, but claim 3 is directed specifically to efficacy "for the treatment of anaphylaxis." Thus, in the context of claim 3, this definition is not complete because it speaks to a biological or medicinal response generally, rather than a biological or medicinal response relevant to anaphylaxis. Thus, in our full construction below, we clarify that the "biological or medicinal response" is one relevant to treatment of anaphylaxis.

Applying the above analysis to claim 3's limitation "provides a plasma epinephrine concentration that is efficacious for the treatment of anaphylaxis," for purposes of this Decision we construe this limitation to mean

provides a plasma epinephrine concentration that elicits the biological or medicinal response in a tissue, system, or individual that (i) is being sought by a researcher, healthcare

provider, or individual, and (ii) is anaphylaxis-related, which may, but need not necessarily, eliminate one, more, or all symptoms of anaphylaxis, and may also prevent progression of anaphylaxis or the appearance of further symptoms.

D. Alleged Anticipation

Petitioner asserts that Potta anticipates claims 1–18 under 35 U.S.C. § 102. Pet. 36. At this stage, Patent Owner limits its arguments to claim 1, and does not specifically argue the dependent claims. *See* Prelim. Resp. 46 (“Because this [dosage] limitation is found in claim 1 of the ’414 patent, and because all other claims depend on claim 1, Potta also cannot anticipate dependent claims 2-18.”).

For the reasons discussed below, on this record we determine that Petitioner has shown a reasonable likelihood of establishing that Potta anticipates at least one of the challenged claims.

1. Legal Standards

“To anticipate, [a] reference must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim.” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008) (internal quotation omitted). However, “a reference need not always include an express discussion of the actual combination to anticipate.” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1344 (Fed. Cir. 2016). “Instead, a reference may still anticipate if that reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination.” *Id.* “[T]he dispositive question regarding anticipation [i]s whether *one skilled in the art* would reasonably understand or infer from the [prior art reference’s] teaching’ that every claim element was disclosed in

that single reference.” *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991)) (emphasis and alterations in original).

As discussed below, on this record we determine that Petitioner has shown a reasonable likelihood that Potta anticipates at least claims 1, 2, 7–10, and 12–17. We have some reservations, however, regarding Petitioner’s anticipation arguments for claims 3–6, 11, and 18, and thus below we provide the parties guidance on our current view of Petitioner’s arguments concerning those claims.

2. Overview of Potta (Ex. 1004)

Potta, titled “Epinephrine Spray Formulations,” is “directed to methods of treating anaphylaxis by administering epinephrine spray formulations to subjects in need of such treatments.” Ex. 1004, code (54), ¶ 1. Potta explains that “[w]hile there are various epinephrine formulations currently available, there remains a need in the art for a quick-onset spray formulation.” *Id.* ¶ 6. Potta discloses that administration of its sprays “preferably . . . occurs via the intranasal route or sublingual route.” *Id.* ¶ 56.

Potta claim 21 relates to aqueous intranasal formulations that include about 0.1% w/w to about 15% w/w epinephrine, and Table 1 exemplifies aqueous formulations comprising 1% w/w epinephrine. *Id.* at claims 1, 19, 21, Table 1. Potta also discloses unit-dose devices that deliver about 100 µL or 200 µL of a formulation in a single spray. *Id.* at ¶¶ 236–37, 242.

Potta details a clinical study wherein a 6 mg intranasal epinephrine formulation was administered to minipigs. *Id.* ¶¶ 258–60. This study compared the pharmacokinetics of the 6 mg epinephrine intranasal formulation (designated “#M1”) and a 0.3 mg intramuscular formulation.

Id. ¶ 260, Tables 56, 57. Potta reports that “[w]hen epinephrine was formulated in #M1 and administered intranasally, a more rapid absorption of epinephrine was observed” compared to the intramuscular administration. *Id.* ¶ 260; *see also id.* at Table 57 (reporting plasma concentrations over time for intramuscular and intranasal administration).

Potta also details another clinical study wherein 3 mg and 6 mg intranasal epinephrine formulations were administered to humans. *Id.* ¶¶ 265–68. This study assessed the bioavailability of 3 mg and 6 mg epinephrine intranasal aqueous and hydroalcoholic formulations compared to a 0.3 mg intramuscular formulation (EpiPen). *Id.* ¶ 266. Potta reports pharmacokinetic profiles for the 6 mg and intramuscular formulations both pre- and post-exposure to seasonal allergens, and concludes that “subjects administered 6 milligrams of epinephrine in a hydroalcoholic formulation of the present invention in the presence of an allergen had a higher C_{max} than all other cohorts.” *Id.* ¶ 266; *see also id.* ¶¶ 267–68, Tables 63–65, Figs. 1–3. Potta concludes that “the bioavailability of intranasal formulations of the present invention is as good or better than that of the intramuscular injection both in subject[s] that are and are not experiencing seasonal allergies.” *Id.* ¶ 269.

3. *Analysis of Independent Claim 1*

We find that Petitioner shows a reasonable likelihood that Potta anticipates claim 1. Pet. 30–34. For example, Petitioner sufficiently demonstrates for purposes of institution that Potta teaches administering aqueous nasal spray pharmaceutical formulations to humans in need of treatment of type-1 allergic reactions, including anaphylaxis. *See, e.g.,* Pet.

30–32 (citing, e.g., Ex. 1004 ¶¶ 1, 56, 69, 242, Table 1, claims 1, 19, 21; Ex. 1002 ¶¶ 243–44, 246–48, 254–59; Ex. 1003 ¶¶ 256–72).

Petitioner also sufficiently demonstrates for purposes of institution that Potta teaches claim 1’s recitations of “about 0.1 mg to 2.4 mg of epinephrine” in a “single dose.” Ex. 1001, 72:21–23. In particular, Potta teaches 1% w/w aqueous epinephrine formulations in Table 1, and a preference for intranasal administration. Ex. 1004, Table 1, ¶ 56. Claim 21 echoes these disclosures by reciting intranasal administration of aqueous epinephrine formulations comprising “from about 0.1% w/w/ to about 15% w/w epinephrine.” *Id.* at claims 1, 19, 21. Potta also teaches unit-dose devices for intranasal administration of epinephrine that deliver a single dose of about 100 µL or 200 µL in a single spray. *Id.* ¶¶ 56–58, 236–37; Pet. 32–34. Based on those disclosures, Petitioner shows a reasonable likelihood of establishing that a person of ordinary skill in the art would have understood Potta as disclosing intranasal epinephrine formulations in Table 1 that correspond to 1 mg/100 µL or 2 mg/200 µL in a single dose, and intranasal epinephrine formulations in claim 21 that correspond to about 0.1–15 mg in a single 100 µL spray or 0.2–30 mg in a single 200 µL spray. Pet. 33–34 (citing, e.g., Ex. 1002 ¶¶ 240–51, 261; Ex. 1003 ¶¶ 263–65, 275). These epinephrine doses fall within or overlap with those recited in challenged claim 1.

Patent Owner focuses its non-anticipation arguments on challenged claim 1’s dosage range (i.e., “between about 0.1 mg and about 2.4 mg of epinephrine or a salt thereof in a single dose”). *See, e.g.*, Prelim. Resp. 41–46. First, Patent Owner argues that Potta does not inherently disclose this dosage range because “Potta explicitly discloses that ‘%w/w’ refers to ‘the

percent weight of the total formulation,”” and lacks information sufficient to convert the claimed weight percents to a total amount of epinephrine that is being dosed. *Id.* at 42 (quoting Ex. 1004 ¶ 66); *see also id.* at 43.

This argument is unavailing, because we do not view Petitioner’s argument as relying on inherent disclosure. Rather, as summarized above, Petitioner relies on Potta’s actual disclosures and how the skilled artisan would understand them—e.g., Potta’s claims 1, 19, and 21 and the formulations in Table 1, viewed in the context of Potta’s disclosure regarding unit-dose devices that deliver a single dose of about 100 µL or 200 µL—to reach challenged claim 1’s dosage range. *See* Pet. 32–34 (citing, e.g., Ex. 1004, claims 1, 21, ¶¶ 56–58, 236–37, 242, Table 1). On this record, Petitioner adequately establishes, for purposes of institution, that a person of ordinary skill in the art reading Potta would have understood the dosage range recited in Potta’s claim 1 to correspond to about 0.1–15 mg epinephrine base in a 100 µL spray, or about 0.2–30 mg epinephrine base in a 200 µL spray. Ex. 1002 ¶¶ 240, 241, 250–53, 260–62; Ex. 1003 ¶¶ 95, 263–65, 267, 274–76.

Patent Owner acknowledges that Potta discloses unit-dose devices that deliver a single dose of 100 µL, but argues that this disclosure “say[s] nothing about delivering these doses *intranasally*.” Prelim. Resp. 43 (citing Ex. 1004 ¶¶ 56–58, 236–37); *see also id.* at 44 (“[N]one of the epinephrine formulations listed in Table 1 are described as being administered intranasally.”). On this record we find this argument unavailing. Anticipation does not require that a reference “include an express discussion of the actual combination to anticipate;” rather, it can teach “that the disclosed components or functionalities may be combined.” *Blue Calypso*,

LLC, 815 F.3d at 1344. Here, Potta teaches a preference for intranasal administration (Ex. 1004 ¶ 56), and Patent Owner has not directed us to anything in Potta that divorces this preference from the disclosed spray devices or from the formulations in Table 1. Indeed, the record elsewhere indicates that “standard metered nasal spray devices” delivered 100 µL of nasal spray. Ex. 1005 ¶¶ 358, 371; *see also* Ex. 1001, 52:12–16 (challenged patent indicating that “[m]etered spray pumps have dominated the nasal drug delivery market since they were introduced,” and “[t]he pumps typically deliver 100 µL (25–250 µl) per spray”). The skilled artisan would read and understand Potta with this well-known background in mind.

Patent Owner also argues that “other disclosures in Potta that allegedly provide for a single dose administered intranasally advocate for much higher dosages than what is claimed in the ’414 patent—at least 3 mg, but preferably 6 mg.” Prelim. Resp. 43 (citing Ex. 1004 ¶¶ 258–60, 265–68); *see also id.* at 44. Patent Owner also asserts that Potta “is clearly directed to administering a dosage of 6 mg epinephrine to achieve effect, not the ‘about 0.1 mg to about 2.4 mg’ range of the challenged claims.” *Id.* at 44–45 (citing, e.g., Ex. 1004 ¶¶ 210–14, 258–69).

These arguments are unavailing. “[A] reference is not limited to the disclosure of specific working examples.” *In re Mills*, 470 F.2d 649, 651 (CCPA 1972). On this record, Patent Owner does not articulate how Potta’s examples relating to intranasal administration of 3 mg and 6 mg epinephrine formulations detract from Potta’s other disclosures, which as discussed above, collectively teach the intranasal administration of epinephrine formulations falling within and overlapping with challenged claim 1’s recited dosage range.

Finally, Patent Owner argues “even assuming *arguendo* that the doses claimed in the ’414 patent are a subset of the broad range disclosed by Potta, Potta does not necessarily anticipate the claims of the ’414 patent” because “[a] claimed range is anticipated by a prior art reference **only ‘if** the reference discloses **a point** within the range.” Prelim. Resp. 45 (citing *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) (emphasis added by Patent Owner). This argument is unavailing, because it ignores that the formulations in Potta Table 1 disclose a point within challenged claim 1’s recited dosage range (i.e., as discussed above, we preliminarily find that skilled artisans would read Potta as teaching 1% w/w epinephrine formulations that correspond to a dose of about 1 mg or 2 mg epinephrine in 100 μ L or 200 μ L, respectively, in the disclosed unit dose devices). See, e.g., Ex. 1003 ¶ 95; see also *Ineos USA LLC*, 783 F.3d at 869 (“When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.”).

With regard to the range recited in Potta’s claim 21, Patent Owner argues that Potta can anticipate “**only if** it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges.” Prelim. Resp. 45 (quoting *Ineos USA LLC*, 783 F.3d at 869 (emphasis added by Patent Owner)). Patent Owner contends that “based on the prior art (e.g., Potta and Srisawat),” a skilled artisan would have expected “that epinephrine operates extremely differently when administered over different dosage ranges, to the point where epinephrine does not operate at all at low doses (the exact opposite of what the ’414 patent claims).” *Id.* at 45–46 (citing Ex. 1004 ¶¶ 258–69; Ex. 1006, Fig. 1).

On this record, Patent Owner’s argument is unavailing. Patent Owner relies on Potta’s clinical data relating to 3 mg and 6 mg intranasal epinephrine formulations (Ex. 1004 ¶¶ 258–69), but as discussed above, Patent Owner does not demonstrate how these data (or anything else in Potta) suggest that intranasal doses lower than 3 mg or 6 mg would lack efficacy. And while Srisawat’s Figure 1 shows no significant systemic absorption of epinephrine for doses under 5 mg, Srisawat expressly acknowledges that formulation could affect absorption, and suggests that surfactants might promote absorption. Ex. 1006, Fig. 1, 4–5. Accordingly, on this record Patent Owner has not established that persons of skill in the art would have expected that “epinephrine does not operate at all” at the doses recited in challenged claim 1. Prelim. Resp. 46.

For the above reasons, on this record we determine that Petitioner has shown a reasonable likelihood of establishing that Potta anticipates claim 1, and on that basis, institute *inter partes* review of all challenged claims. See *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1358 (2018); 37 C.F.R. § 42.108(a) (“When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims.”). To provide the parties guidance, below we address Petitioner’s anticipation arguments as applied to dependent claims 2–18.

4. *Analysis of Dependent Claims 2–18*

On this record we find that Petitioner comes forward with information sufficient to show a reasonable likelihood that Potta anticipates claims 2, 7–10, and 12–17. See Pet. 36–42.

As to claim 3, however, we have reservations as to whether Petitioner has established a reasonable likelihood that Potta anticipates this claim (and

claims 4–6 and 18, which depend directly or indirectly from claim 3). Claim 3 as construed herein requires that the intranasal administration provides a plasma epinephrine concentration that elicits a biological or medicinal response that (i) is being sought by a researcher, healthcare provider, or individual, and (ii) is anaphylaxis-related. *See supra* Section II.C.2; Ex. 1001, 72:33–37. Petitioner contends that if claim 3 is limiting, Potta inherently anticipates it because “a plasma concentration that is efficacious for the treatment of anaphylaxis would occur upon administration of the Potta formulations.” Pet. 35 (citing Ex. 1002 ¶¶ 270–73; Ex. 1003 ¶¶ 286–87; *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377–78 (Fed. Cir. 2005)).

On this record, we are skeptical of Petitioner’s theory. Although the measure of efficacy required by claim 3 as construed herein is quite broad, Petitioner does not address adequately what plasma concentrations would occur upon administration of Potta’s formulations, and thus at a minimum it is not clear whether Petitioner has established that such plasma concentrations would necessarily elicit a biological or medicinal response being sought by a researcher, healthcare provider, or individual. *Perricone*, 432 F.3d at 1376. Petitioner’s cited expert testimony (Ex. 1002 ¶¶ 270–73; Ex. 1003 ¶¶ 286–87) appears to lack factual corroboration. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) (“[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations.”).

We also have reservations about whether Petitioner has demonstrated a reasonable likelihood that Potta anticipates claim 11. Claim 11 depends

indirectly from claim 1, and in pertinent part requires that the claimed formulation comprise specific amounts of BKC as an absorption enhancement agent. Ex. 1001, 73:31–43. Petitioner correctly asserts that Potta discloses the use of absorption enhancers, including oleic acid and EDTA. Pet. 37 (citing Ex. 1004 ¶¶ 80, 86, Table 1; Ex. 1002 ¶¶ 288–91). Petitioner does not assert that Potta expressly discloses using BKC as an absorption enhancer, but instead argues that skilled artisans would have “immediately envisioned using BKC in Potta’s claim 21 and 1% w/w epinephrine formulations,” in the amounts Potta provides for permeation enhancers generally, which Petitioner argues encompass the claimed amounts. *Id.* This is because, Petitioner contends, (1) Potta states that suitable permeation enhancers are “not limited to” those listed and provides amounts of permeation enhancers; (2) Potta discloses epinephrine sprays containing BKC;¹³ and (3) BKC was a well-known absorption enhancing agent. *Id.* at 37–38 (quoting Ex. 1004 ¶ 86; citing *id.* at Tables 28, 62; Ex. 1002 ¶¶ 292–95; Ex. 1005; *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1383 (Fed. Cir. 2015)), 40 (citing Ex. 1004 ¶ 85; Ex. 1002 ¶¶ 317–22).

We are not presently persuaded by Petitioner’s arguments. Potta does not expressly disclose using BKC as an absorption enhancer. Nevertheless, anticipation may still arise if a reference describes a “definite and limited class” and a person of ordinary skill in the art would “at once envisage each member of this limited class.” *In re Petering*, 301 F.2d 676, 681 (CCPA 1962). Here, Petitioner at best establishes that BKC was a known absorption

¹³ Potta expressly discloses using BKC as a preservative. Ex. 1004 ¶ 91.

enhancer. *See, e.g.*, Ex. 1005 ¶ 243. This does not, however, equate to Potta teaching a “definite and limited class” of absorption enhancers that includes BKC. The Petition does not appear to address, for example, the size or members of the alleged “definite and limited class.” *See, e.g., Wasica Finance GmbH v. Continental Automotive Systems, Inc.*, 853 F.3d 1272, 1285–86 (Fed. Cir. 2017) (rejecting argument that skilled artisan would “at once envisage each member” of a limited class where underlying *inter partes* review petition failed to identify the genus, establish its size, or name the pertinent species); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274–75 (Fed. Cir. 2017) (explaining that the “at once envisage” test “does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would ‘at once envisage’ the missing limitation”). The Petition also does not appear to address why a skilled artisan would have understood Potta’s general disclosure regarding amounts of absorption enhancers to be applicable to BKC in particular. Accordingly, we have reservations about whether Petitioner has demonstrated a reasonable likelihood that Potta anticipates claim 11.

The record would benefit from development of these issues at trial.

E. Alleged Obviousness Over Potta, Maggio, and Munjal

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over Potta, Maggio, and Munjal. Pet. 44–54. At this stage, Patent Owner argues claims 1–20 as a group, and does not specifically address Petitioner’s obviousness arguments for the dependent claims. *See generally* Prelim. Resp. 46–50.

For the reasons discussed below, on this record we determine that Petitioner has shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Potta, Maggio, and Munjal.

1. Legal Standards

A claim is unpatentable as obvious “if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103; *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on 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 ordinary skill in the art; and (4) any objective indicia of nonobviousness.¹⁴ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An obviousness determination requires finding “a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

¹⁴ Petitioner anticipates that Patent Owner may rely on certain objective indicia of nonobviousness, and thus preliminarily (and preemptively) addresses such potential arguments in the Petition. Pet. 61–62. On this record, however, Patent Owner does not rely on objective indicia or respond to Petitioner’s preemptive arguments. *See generally* Prelim. Resp. Given the incomplete record, we do not address Petitioner’s preemptive arguments at this stage, but rather will analyze any objective indicia arguments that develop on the full trial record.

2. *Overview of Maggio (Ex. 1005)*

Maggio, titled “Compositions for Drug Administration,” relates “to compositions containing a pharmaceutically active ingredient and an alkylsaccharide.” Ex. 1005, code (54), ¶ 3. Maggio explains that although therapeutic agents are often combined with surfactants, surfactants can irritate mucosal membranes and denature proteins. *Id.* ¶ 5. Maggio describes an ideal surfactant as one that stabilizes a therapeutic agent, is non-toxic and non-irritable, has antibacterial activity, and enhances the absorption of the therapeutic agent through membrane barriers. *Id.*

Maggio describes compositions that include alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent, and methods of administering the compositions, including via nasal delivery. *Id.* ¶ 12. Maggio discloses DDM as a preferred alkyl glycoside. *Id.* ¶ 48. Maggio provides clinical data including from a comparison of the pharmacokinetics of intranasal formulations of sumatriptan with and without DDM, and from the administration of phenylephrine oral tablets with DDM in canines. Ex. 1005 ¶¶ 353–56, 358–69, Fig. 12.

3. *Overview of Munjal (Ex. 1020)*

Munjal is titled “A Randomized Trial Comparing the Pharmacokinetics, Safety, and Tolerability of DFN-02, an Intranasal Sumatriptan Spray Containing a Permeation Enhancer, With Intranasal and Subcutaneous Sumatriptan in Healthy Adults.” Ex. 1020, 1. Munjal discloses clinical studies that evaluate “the impact of 1-O-n-Dodecyl- β -D-Maltopyranoside (DDM, Intravail A-3TM), a permeation enhancer,” on the absorption profile for intranasally-administered sumatriptan. In particular, Munjal compares the pharmacokinetics of DFN-02 (“a novel intranasal

agent comprised of sumatriptan 10 mg plus 0.20% DDM”), with that of commercially available intranasal sumatriptan 20 mg. *Id.* at 1, 3. Munjal states that absorption “was markedly more rapid” with DFN-02 than with the sumatriptan 20 mg product. *Id.* at 5, Fig. 1, Table 1.

4. *Brief Summary of Petitioner’s Arguments*

Petitioner asserts that given the known drawbacks of intramuscular injections to treat anaphylaxis, skilled artisans would have been motivated to use alternate means of administration, such as Potta and Srisawat’s intranasal epinephrine sprays. Pet. 44–45. Petitioner also contends that given epinephrine’s dose-dependent side effects and narrow therapeutic window, skilled artisans would have been motivated “to pursue the low dose epinephrine nasal formulations disclosed in the prior art,” such as the 1% w/w epinephrine (i.e., 1 mg/100 µl) formulations taught in Potta. *Id.* at 22 – 23 (citing, e.g., Ex. 1002 ¶¶ 88–94, 367; Ex. 1003 ¶¶ 94–107, 316–18), 49; *see also id.* at 6, 21 (citing, e.g., Ex. 1041, 6, 8, 13, Fig. 4; Ex. 1014, 11; Ex. 1052, 3–4; Ex. 1056, 2).

Petitioner also asserts that “[b]ecause treatment of anaphylaxis requires rapid onset to avoid death or complications, POSAs were motivated to use absorption enhancement agents.” *Id.* at 6; *see also id.* at 45. Skilled artisans would have turned in particular to DDM, Petitioner says, including because it is “safe, non-toxic, and non-irritating, while still promoting rapid absorption of small molecules across the nasal mucosa[.]” *Id.* at 45 (citing, e.g., Ex. 1002 ¶¶ 374–75; Ex. 1003 ¶¶ 330–47); *see also id.* at 49–51. Petitioner asserts that based on prior art such as Maggio and Munjal, skilled artisans would have “understood that using DDM increased the bioavailability of small molecules in intranasal formulations, allowing for

reduced doses and side effects.” *Id.* at 47 (citing, e.g., Ex. 1002 ¶¶ 373–96, 404–07; Ex. 1003 ¶¶ 352–53).

Based on the above considerations, Petitioner argues that skilled artisans would have been motivated to optimize the “low dose” intranasal formulations taught in Potta’s Table 1 and claim 21 by adding an absorption enhancer such as DDM. *Id.* at 45, 48–51.

5. *Analysis of Independent Claim 1*

At this stage of the proceeding, Petitioner comes forward with information sufficient to show a reasonable likelihood that claim 1 would have been unpatentable as obvious over Potta, Maggio, and Munjal. Pet. 48–51.

At the outset we note that although challenged claim 1 does not expressly recite an absorption enhancer, Petitioner’s obviousness arguments include assertions that a skilled artisan would have been motivated to optimize Potta’s formulations by including DDM as an absorption enhancer. *See, e.g.*, Pet. 49 (“Here, POSAs would have pursued the low dose formulations in Potta and understood them to work with absorption enhancement agents (though none are required by claim 1) to practice the claimed method.”); *id.* at 49–51 (addressing DDM). Thus, although on this record Petitioner has shown a reasonable likelihood that Potta teaches each limitation of claim 1 (*see supra* Section II.D.3; *see also* Pet. 30–34 (mapping Potta’s disclosures to the limitations of claim 1)), our analysis of Petitioner’s obviousness argument requires additional considerations.

On this record, Petitioner sufficiently establishes for purposes of institution that Potta expressly teaches inclusion of an absorption enhancer in its formulations. *See, e.g.*, Ex. 1004 ¶¶ 80, 85–86 (identifying permeation

enhancers, including EDTA); Table 1 (formulations include EDTA); *see also* Pet. 49 (citing, e.g., Ex. 1004 ¶¶ 80, 86, Table 1, claim 21; Ex. 1002 ¶¶ 136, 370, 390; Ex. 1003 ¶¶ 145, 322). Petitioner also sufficiently demonstrates for purposes of institution that a person of ordinary skill in the art would have been motivated with a reasonable expectation of success to select DDM as the absorption enhancer. For example, the prior art taught the combination of DDM and epinephrine to enhance epinephrine absorption across mucosal membranes in ophthalmic, buccal, lingual, and sublingual formulations. Pet. 6–7, 47–48; Ex. 1002 ¶¶ 109–10, 377; Ex. 1003 ¶ 352; Ex. 1021, 9:15–38; Ex. 1022, code (57), ¶¶ 53, 102. Additionally, Maggio suggested the use of DDM with epinephrine. Pet. 48 (citing, e.g., Ex. 1002 ¶ 377; Ex. 1003 ¶ 352; Ex. 1005 ¶ 356). Maggio and Munjal also demonstrate the advantages of using DDM (albeit with other molecules) to increase uptake and bioavailability across mucosal membranes. Pet. 49–51. Accordingly, on this record, Petitioner establishes a reasonable likelihood that Potta teaches all limitations of claim 1, and that a person of ordinary skill in the art would have been motivated to add an absorption enhancer, and particularly DDM, to Potta’s formulations with a reasonable expectation of success.

Thus, on this record we find Petitioner’s showings sufficient to establish that claim 1 is likely unpatentable as obvious. At this stage, Patent Owner focuses its arguments on claim 1, and does not specifically dispute Petitioner’s obviousness arguments for the dependent claims. *See generally* Prelim. Resp. 46–50.

Patent Owner argues that “Potta teaches away from the low doses” recited in claim 1. Prelim. Resp. 47. This is because, Patent Owner

contends, “the higher dose of epinephrine (6 mg) was reported by Potta to be more effective than the lower doses (3 mg),” and thus “a skilled artisan reviewing Potta would not have been motivated to use an even lower dose.”

Id. On this record, we do not agree with Patent Owner that Potta’s in vivo data would have negated a motivation to use Potta’s lower dose formulations (e.g., in Potta Table 1) intranasally. First, Potta does not appear to expressly report that the 6 mg intranasal dose was “more effective than the lower dose (3 mg),” as Patent Owner contends. *Id.* Rather, although Potta tested both 3 mg and 6 mg intranasal formulations in humans, Potta reports only the data for the 6 mg formulations. Ex. 1004 ¶¶ 210–14, 268, Tables 63–65, Figs. 1–3. On this record Patent Owner does not point us to any express statement in Potta indicating that the 3 mg dose was ineffective, or that the 6 mg dose was more effective than the 3 mg dose.

Second, on this record, Patent Owner does not adequately explain how Potta’s data, standing alone, suggest that the 1% w/w epinephrine formulations (corresponding to a dose of about 1 mg or 2 mg epinephrine in 100 µL or 200 µL, respectively) would lack efficacy in the broad category of claimed mammals. Even if Potta’s disclosure overall suggests to a skilled artisan that a 6 mg intranasal dose would be *more* effective than lower intranasal doses in humans, Patent Owner does not point to any disclosure in Potta that indicates a lack of efficacy for lower intranasal doses. *See In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (“[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.”). Moreover, even if Potta teaches or suggests that a higher (6 mg) dose is more effective than lower doses, this alone does not

necessarily mean that skilled artisans would have been led away from lower dose formulations. Patent Owner does not account for Petitioner’s argument regarding the expected increased bioavailability of the lower dose formulations resulting from the addition of an absorption enhancer such as DDM. *See, e.g.*, Ex. 1002 ¶¶ 373–83; Ex. 1005 ¶ 360; Ex. 1020, 5–6.

Patent Owner next argues that neither Maggio nor Munjal “fill[s] [Potta’s] gap” because they do not disclose the “claimed lower dose of epinephrine.” Prelim. Resp. 47–48. This argument is not persuasive, because it focuses on the teachings of the individual references. *In re Keller*, 642 F.2d 413, 426 (CCPA 1981) (“[O]ne cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references.”). As discussed above, Petitioner relies on Potta, not Maggio or Munjal, as disclosing epinephrine doses within the claimed range.

Patent Owner also contends that “Petitioner has failed to supply a credible reason” to combine Potta, Maggio, and Munjal, given that Maggio and Munjal teach the use of DDM with triptans (e.g. sumatriptan) and opioids, not with epinephrine. Prelim. Resp. 48. Patent Owner correctly notes that epinephrine, sumatriptan, and opioids have different structures and indications. *Id.* at 48–49. But Patent Owner’s narrow focus on the different structures and indications overlooks both Petitioner’s arguments regarding other formulations (ophthalmic, buccal, lingual, sublingual) that combined epinephrine and DDM, and Maggio’s suggestion to use DDM with epinephrine, as summarized above. On this record, these factors—together with Maggio and Munjal’s teachings that DDM increases uptake and bioavailability (albeit demonstrated with other molecules)—sufficiently

support a motivation to combine Potta's epinephrine formulations with DDM.

Patent Owner also argues that “there is nothing in Maggio ’145 or Munjal that indicates that alkylsaccharides (or DDM in particular) would have an effect on intranasal administration of *epinephrine*.” *Id.* at 49–50. On this record this argument is unavailing, because as discussed above, Petitioner cites other prior art that taught the combination of DDM and epinephrine to enhance epinephrine absorption across mucosal membranes, including in ophthalmic, buccal, lingual, and sublingual formulations. *See* Pet. 47–48.

For the above reasons, Petitioner has established a reasonable likelihood of prevailing in demonstrating that claim 1 would have been obvious over Potta, Maggio, and Munjal.

6. *Analysis of Dependent Claims 2–20*

As noted above, at this stage Patent Owner does not specifically dispute Petitioner's obviousness arguments for any dependent claim. Nevertheless, to provide guidance to the parties, we address the dependent claims. On this record, we find that Petitioner comes forward with information sufficient to show a reasonable likelihood that dependent claims 2, 7–9, and 12–17 would have been obvious over Potta, Maggio, and Munjal. *See* Pet. 51–52. We have reservations, however, as to whether Petitioner has established a reasonable likelihood that claims 3–6, 10, 11, and 18–20 would have been obvious over Potta, Maggio, and Munjal. We explain our reasoning regarding claims 3–6, 10, 11, and 18–20 below.

With respect to claim 3 and claims that depend therefrom (i.e., claims 4–6 and 18–20), we question the adequacy of Petitioner’s arguments. As construed herein, claim 3 requires that the claimed method

provides a plasma epinephrine concentration that elicits the biological or medicinal response in a tissue, system, or individual that (i) is being sought by a researcher, healthcare provider, or individual, and (ii) is anaphylaxis-related, which may, but need not necessarily, eliminate one, more, or all symptoms of anaphylaxis, and may also prevent progression of anaphylaxis or the appearance of further symptoms.

See supra Section II.C.2.

Petitioner asserts that combining Potta’s formulations with DDM would have “inherently” “elicit[ed] a biological response.” Pet. 52 (citing Ex. 1002 ¶¶ 416–21; Ex. 1003 ¶¶ 366–68). Even assuming Petitioner has established that a person of ordinary skill would have expected DDM to increase epinephrine’s uptake and absorption, we have reservations about whether Petitioner demonstrates that a skilled artisan would have reasonably expected the method to necessarily result in a plasma epinephrine concentration that elicits a biological or medicinal response as claimed. Again, we recognize that the measure of efficacy required by claim 3 as construed herein is quite broad. However, the cited expert testimony (Ex. 1002 ¶¶ 416–21; Ex. 1003 ¶¶ 366–68) does not appear to address the plasma concentrations that would have been expected upon administering Potta’s formulations with DDM, or otherwise provide a basis for concluding that Potta’s formulations with DDM would have “inherently” “elicit[ed] a biological response” related to anaphylaxis.

Petitioner also asserts that Maggio and Munjal “confirm[.]” that Potta’s formulations with DDM would elicit a biological response, because

these references show that DDM “provide[s] rapid and increased absorption.” Pet. 52 (citing Ex. 1002 ¶¶ 405–06, 418–19; Ex. 1003 ¶¶ 353–54, 366–68). However, even if DDM provides rapid and increased absorption for other small molecules such as phenylephrine and sumatriptan (*see, e.g.*, Ex. 1002 ¶ 405), the pertinent question here is whether the cited prior art would have provided a skilled artisan with a reasonable expectation that adding DDM to Potta’s formulations would result in a plasma epinephrine concentration that elicits the claimed biological or medicinal response. On this record, we are unconvinced that Maggio and Munjal answer this question, because Petitioner has not demonstrated sufficiently that what applied to phenylephrine and sumatriptan would have also applied to the same extent to the claimed amounts of epinephrine. Indeed, the record reflects that “[e]ach drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential.” Ex. 1064, 17.

Petitioner also points to data in Srisawat and Potta resulting from the administration of 5 mg and 6 mg intranasal epinephrine formulations, respectively (Pet. 46), but on this record, Petitioner fails to adequately explain how these data would have provided a reasonable expectation that adding DDM to lower dose formulations would have led to a reasonable expectation of eliciting the claimed biological or medicinal response. Ex. 1064, 17.

We also question the adequacy of Petitioner’s arguments for claim 10, which indirectly depends from claim 1. In pertinent part claim 10 recites “about 0.005% (w/v) to about 2.5% (w/v) dodecyl maltoside.” Petitioner asserts that Maggio and Munjal teach amounts of DDM that overlap with or

are encompassed by claim 10, and specifically teach using 0.18% and 0.20% DDM in an intranasal sumatriptan formulation. Pet. 53. To show obviousness, however, it is not enough to merely show that the prior art includes references disclosing each limitation in a challenged claim. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Here, the Petition appears to be wanting for a sufficient reason why a person of ordinary skill would have been motivated to use the amounts of DDM taught in Maggio and Munjal’s sumatriptan formulations in Potta’s epinephrine formulation. *See, e.g., Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir. 2017) (“In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination.”). The Petition notes that both sumatriptan and epinephrine are small molecules (Pet. 53), but on this record we find this to be too tenuous a reason to have motivated a skilled artisan to use the specific amounts of DDM used in the sumatriptan formulations in an epinephrine formulation.

Claim 11 indirectly depends from claim 1, and recites that the absorption enhancement agent is BKC in certain amounts, either alone or in combination with one or more other absorption enhancement agents.

Petitioner argues:

Maggio ’145 disclosed ‘surfactant[s]’ and ‘mucosal delivery-enhancing agents’ including BKC in specific amounts. Ex. 1002 ¶¶470. Given this, the limitations of claim 11 would have been obvious. *Id.* ¶¶464-77.

Pet. 53. Because claim 11 ultimately depends from claim 1, we understand Petitioner's argument to be that a person of ordinary skill in the art would have included both DDM and BKC in Potta's formulations. *See also* Ex. 1002 ¶ 467 (arguing that skilled artisans would have been motivated to use BKC and DDM with Potta's formulations). We have concerns as to whether the Petition sufficiently articulates a reason why a person of ordinary skill in the art would have been motivated to use the particular combination of BKC and DDM as absorption enhancers in Potta's formulation, and the claimed amounts of BKC in this combination.¹⁵

For the above reasons, we have reservations regarding whether Petitioner has demonstrated a reasonable likelihood of showing that claims 3–6, 10, 11, and 18–20 would have been obvious over Potta, Maggio, and Munjal. At trial, the record would benefit from development of the issues highlighted above.

F. Alleged Obviousness Over Srisawat, Maggio, and Munjal

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over Srisawat, Maggio, and Munjal. Pet. 54–60. At this stage, Patent Owner argues claims 1–20 as a group, and does not specifically address Petitioner's obviousness arguments for the dependent claims. *See generally* Prelim. Resp. 50–51.

For the reasons discussed below, on this record we have reservations about whether Petitioner has shown a reasonable likelihood of establishing

¹⁵ To the extent Petitioner later asserts that such a motivation to combine is identified in evidence that is cited in the Petition, we remind Petitioner that 37 C.F.R. § 42.6(a)(3) prohibits the incorporation by reference of arguments from one document into another document.

that claims 1–20 are unpatentable as obvious over Srisawat, Maggio, and Munjal.

1. *Overview of Srisawat (Ex. 1006)*

Srisawat is titled “A preliminary study of intranasal epinephrine administration as a potential route for anaphylaxis treatment.” Ex. 1006, 1. Srisawat states that “[t]he intranasal (IN) administration of epinephrine could be an alternative route for anaphylaxis treatment,” but that intranasal epinephrine absorption data in humans are lacking. *Id.* Srisawat thus describes a study wherein various epinephrine doses (0.3, 0.6, 1.25, 2.5, and 5 mg) were administered intranasally to five healthy human adults. *Id.* at 2. The intranasal epinephrine sprays used in the study were freshly prepared by dissolving epinephrine bitartrate in saline. *Id.* The subjects were also administered (in a separate arm of the study) an intramuscular (IM) injection of 0.3 mg epinephrine. *Id.* Plasma epinephrine levels at baseline and at time points up to 120 minutes after administration were determined. *Id.*

Srisawat Figure 1 is reproduced below:

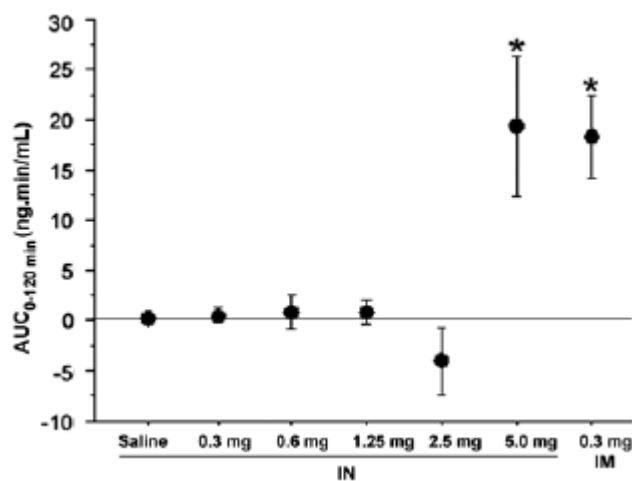


Figure 1. The area under the plasma concentration versus time curve at time

0 – 120 minutes ($AUC_{0-120 \text{ min}}$) of epinephrine absorption at different dosages and routes of administration. The plots are shown as mean \pm SEM. An asterisk indicates a significant difference compared with the IN saline ($p < 0.05$, Mann-Whitney test).

Figure 1 compares the AUC values for each of the epinephrine formulations administered in the study. Consistent with the data reported in Figure 1, Srisawat states that “[s]ignificant systemic absorption of epinephrine via IN route was observed only at the dose of 5 mg, and the absorption thereof was comparable to that of IM epinephrine.” *Id.* at 1. Srisawat states that as compared to intramuscular injection, the slower epinephrine absorption through the intranasal route “is not unexpected, as the drug has to diffuse across the nasal epithelial barrier to reach the systemic circulation.” *Id.* at 4. According to Srisawat, this could “explain a much higher IN dose (5 mg) required to achieve systemic absorption comparable to the IM route at 0.3 mg.” *Id.*

Srisawat recognizes that the formulation could affect intranasal absorption (*id.*), and suggests that “[u]sing bile salt or surfactant as a vehicle might also promote the nasal absorption of epinephrine because they have been shown to work well in a dog model” (*id.* at 5).

2. Analysis

As discussed above (*see supra* Section II.E.4), Petitioner contends that persons of ordinary skill in the art would have sought to optimize low dose intranasal epinephrine formulations. Applying this premise to its Srisawat-based arguments, Petitioner contends that skilled artisans, “understanding [the] side effects posed by higher [epinephrine] dosing and looking to

optimize intranasal dosing (e.g., the 1.25 or 2.5 mg Srisawat formulations), would have looked to absorption enhancement agents to provide rapid onset and increase the systemic bioavailability with a lower dose.”¹⁶ Pet. 55 (citing, e.g., Ex. 1002 ¶¶ 541–42, 545–61; Ex. 1003 ¶¶ 418–22). Petitioner contends that “Srisawat taught the addition of surfactant to increase uptake and absorption, and Maggio ’145 and Munjal directed POSAs to surfactants that are alkylglycosides, such as DDM.”¹⁷ *Id.* at 56 (citing Ex. 1002 ¶¶ 147–68, 532–33, 541–42, 545–61; Ex. 1003 ¶¶ 157–76, 391–92, 406–20). According to Petitioner, skilled artisans would have reasonably expected that combining Srisawat’s 1.25 mg and 2.5 mg epinephrine formulations with DDM would have “‘elicit[ed] a biological response’ when administered to a mammal as claimed in the ’414 patent.” *Id.* at 57 (citing Ex. 1003 ¶¶ 393–428; Ex. 1002 ¶¶ 531–69).

Patent Owner responds that Srisawat teaches away from the claimed dose range (“between about 0.1 mg and about 2.4 mg of epinephrine, or a salt thereof in a single dose”) because despite testing intranasal epinephrine

¹⁶ Petitioner contends that “[t]he 2.5 mg formulation of Srisawat falls within the claimed range because the claimed range includes ‘*about* 2.4 mg’ and ‘*about*’ is defined in the [’414] patent as +/- 20% of the recited value, which would cover up to 2.88 mg.” Pet. 57 n.7 (citing Ex. 1002 ¶ 560); *see also* Ex. 1001, 34:43–52. Patent Owner does not address this contention, and on this record, we agree with Petitioner.

¹⁷ We again note that although challenged claim 1 does not recite any limitations related to an absorption enhancer, Petitioner’s obviousness arguments for all claims in this ground include assertions that a person of ordinary skill in the art would have been motivated to optimize Srisawat’s formulations by including DDM as an absorption enhancer. *See, e.g.*, Pet. 55–56.

doses at 0.3, 0.6, 1.25, 2.5, and 5 mg, Srisawat observed significant systemic absorption at only the 5 mg dose. Prelim. Resp. 50–51 (citing, e.g., Ex. 1001, Figs. 1–2, 14:58–15:56; Ex. 1006, Fig. 1, 3).

On this record, Petitioner does not persuade us that a person of ordinary skill in the art would have been motivated to optimize the 1.25 mg and 2.5 mg epinephrine doses disclosed in Srisawat. As discussed above, Srisawat observed significant systemic absorption of epinephrine at only the 5 mg dose. *See supra* Section II.F.1; Ex. 1006, Fig. 1, 3. Thus unlike Potta, which we preliminary find did not teach or suggest any drawbacks to using its lower dose epinephrine formulations, here Srisawat expressly teaches that its lower doses did not achieve significant systemic absorption. And although Srisawat recognized that using a surfactant might “promote the nasal absorption of epinephrine” and suggested investigating different nasal spray formulations (Ex. 1006, 5), it nowhere suggested lowering the dose to account for any enhanced absorption. Rather, Srisawat expressly suggested repeating the study at doses of “5 mg **or higher** to confirm the reproducibility of these findings **and to obtain the optimal IN doses.**” *Id.* (emphases added); *see also* Prelim. Resp. 51. We preliminarily find that Maggio and Munjal do not overcome these issues. Even if DDM allowed a dose reduction for sumatriptan, Petitioner has not persuaded us on this record that a person of ordinary skill in the art would have reasonably expected that a parallel dose reduction would have been achievable with epinephrine.

The record would benefit from development of these issues at trial.

G. *Notices*

At this stage of the proceeding, the Board has not made a final determination regarding the patentability of any challenged claim. Thus, our view with regard to any conclusion reached in the foregoing analysis could change upon completion of the record.

The Board will deem waived any issue not raised in a timely response to the Petition, or as permitted in another manner during trial, even if asserted in the Preliminary Response or discussed in this Decision.

Nothing in this Decision authorizes Petitioner, in a manner not otherwise permitted by the Board's rules, to supplement the information pertaining to any ground advanced in the Petition.

III. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is instituted based on all grounds asserted 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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Patent 10,682,414 B2

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