

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC. and ALVOTECH HF,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: PGR2025-00085
U.S. Patent No. 12,168,036

PATENT OWNER'S DISCRETIONARY DENIAL BRIEF

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MPEP §§ 2163, 2163.05 (9th ed. Rev. Jan. 2024).....	16

TABLE OF EXHIBITS

Exhibit	Description
2001	Excerpts from the File History of U.S. Appl. No. 17/384,070
2002	US 2018/0326126 (“Fiedler ’126”)
2003	Australian Dep’t of Health & Human Aging, Australian Public Assessment Report for Aflibercept (July 2012) (“AusPAR”)
2004	Ameya U. Borwankar et al., <i>Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine.HCl and Arginine.Glutamate</i> , 55 Ind. Eng. Chem. Rsch. 11225 (2016) (“Borwankar”)
2005	Neal Whitaker et al., <i>A Formulation Development Approach to Identify and Select Stable Ultra-High-Concentration Monoclonal Antibody Formulations with Reduced Viscosities</i> , 106 J. Pharmaceutical Scis. 3230 (2017) (“Whitaker”)
2006	Ameya U. Borwankar et al., <i>Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine.HCl and Arginine.Glutamate: Supplementary Information</i> , 55 Ind. Eng. Chem. Rsch. 11225 (2016) (“Borwankar SI”)
2007	Eylea HD [®] Highlights of Prescribing Information (Oct. 2024)
2008	AbbVie, <i>Allergan, an AbbVie Company, and Molecular Partners Receive Complete Response Letter from FDA on Biologics License Application for Abicipar Pegol</i> , AbbVie News Center (June 26, 2020), https://news.abbvie.com/2020-06-26-Allergan-an-AbbVie-Company-and-Molecular-Partners-Receive-Complete-Response-Letter-from-FDA-on-Biologics-License-Application-for-Abicipar-pegol (“AbbVie PR”)
2009	Rod McNeil, <i>Advances and Developments in Medical Retina</i> , 25 Eye News 1 (2019) (“McNeil”)

2010	Rehan M. Hussain & Thomas A. Ciulla, <i>Emerging Vascular Endothelial Growth Factor Antagonists to Treat Neovascular Age-Related Macular Degeneration</i> , 22 Expert Op. Emerging Drugs 235 (2017) (“Hussain”)
2011	Angus Liu, <i>Novartis Calls off 3 Beovu Trials Testing More Frequent Dosing on Concerns of Vision-Threatening Side Effect</i> , FiercePharma (June 1, 2021) (“Liu”)
2012	Beovu Label (2024)
2013	Philip J. Rosenfeld & David J. Browning, <i>Editorial: Is This a 737 Max Moment for Brolucizumab?</i> , 216 Am. J. Ophthalmology A7 (2020) (“Rosenfeld”)
2014	J. Gaudreault et al., <i>Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration</i> , 46 Invest. Ophthalmol Vis. Sci. 726 (2005) (“Gaudreault”)

I. Preliminary Statement

Alvotech seeks institution of a proceeding that would wastefully revisit references and unpatentability arguments previously considered and overcome during prosecution. Although it may disagree with the Examiner's conclusions, Alvotech does not—and cannot—show any error material to patentability. The Director should exercise his discretion under 35 U.S.C. § 325(d) to deny institution.

Regeneron's U.S. Patent 12,168,036 ("036 patent") discloses and claims methods of treating angiogenic eye disorders by administering high-concentration, low-volume, low-viscosity formulations of VEGF receptor fusion proteins. Four of Alvotech's five grounds allege obviousness over references the Examiner already considered during prosecution or that are substantially similar to, and cumulative of, art the Examiner considered. Alvotech's remaining written-description ground re-raises the precise argument that formed the basis of the Examiner's rejection of the pending claims—which the Examiner ultimately withdrew following Regeneron's amendment and argument. Alvotech makes no attempt to show material error in the Examiner's consideration of the references, and Alvotech's written-description arguments fall far short of the requisite showing that no reasonable examiner could have allowed the claims. As explained herein, discretionary denial is appropriate.

II. Background

'036 Patent. Angiogenic eye disorders can lead to vision loss and blindness.

Ex.1001 ('036 patent), 8:22-37, 29:19-50. These disorders involve abnormal blood vessel growth, a process termed angiogenesis, which is driven by the binding of vascular endothelial growth factor (“VEGF”) to VEGF receptors in the eye. *Id.* To treat these disorders, patients receive repeated injections into the eye of ophthalmic formulations containing antibodies or fusion proteins—like Regeneron’s fusion protein aflibercept—which block VEGF binding. *Id.*, 2:5-10, 15:51-67, 29:19-30:5.

Prior treatments undesirably required frequent intravitreal injections on a monthly or bimonthly basis, imposing a “significant treatment burden on patients.” *Id.*, 51:18-26. Although “[h]igher concentration antibody formulations ... allow[ed] for shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility,” *id.*, 1:55-58, such high-concentration formulations also could lead to a host of challenges. Higher concentrations make it “more difficult ... to maintain the proper activity and delivery parameters for the formulation,” with such formulations “often contend[ing] with increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability.” *Id.*, 1:58-65. As a result, “few ... pharmaceutically acceptable [high-concentration] formulations have been developed.” *Id.*, 1:65-2:1. Indeed, several high-concentration products have failed because they exhibited poor safety and increased inflammation. *See, e.g.*, Ex.2008 (AbbVie PR) at 1 (“unfavorable benefit-risk ratio”

due to “intraocular inflammation” from abicipar); Ex.2009 (McNeil) at 2; Ex.2010 (Hussain) at 6; Ex.2011 (Liu) at 1; Ex.2012 (Beovu Label 2024) at 1, 8; Ex.2013 (Rosenfeld) at 1 (based on inflammation and “irreversible severe vision loss,” advising that “intravitreal injections of brolucizumab should stop”); Ex.2014 (Gaudreault) at 2-3 (increased inflammation for 40 vs. 10 mg/ml ranibizumab).

Overcoming these difficulties, the inventors of the '036 patent achieved high-concentration aflibercept formulations while avoiding issues with viscosity, stability, and inflammation that plagued other high-concentration formulations. *E.g.*, Ex.1001, 2:20-40, 13:20-41, 20:31-41, 38:26-40:11, 42:14-22. One such formulation is Regeneron’s groundbreaking biologic product Eylea HD®—a 114.3 mg/ml aflibercept solution with an injection volume of 0.07 ml for an 8 mg dose—which has the durability to be administered less frequently than Eylea® (once every 8 to 16 weeks following three initial monthly doses). Ex.2007 (Eylea HD Label) at 1. The '036 patent’s claim 1 recites a method of treating angiogenic eye disorders “comprising administering, intravitreally ... in a volume of about 100 microliters or less, at least about 8 mg of a VEGF receptor fusion protein ... in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20 °C.”

Prosecution of the '036 Patent. The claims originally recited “[a] method for treating an angiogenic eye disorder ... comprising administering an intravitreal

injection of at least about 8 mg of a VEGF receptor fusion protein” Ex.2001 (Excerpted File History) at 2. The Examiner initially rejected those claims as inadequately described, *id.* at 230, reasoning that “the claim recites a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein.” *Id.* at 231. Because the specification discloses the importance of “L-arginine ... [for] increas[ing] the stability of high concentrations of the VEGF trap Aflibercept,” the Examiner found “adequate written description for stable, high concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine based buffer, and L-arginine,” but not for the pending claims. *Id.*

In response, the applicant amended the claims to recite a volume of 100 microliters or less, a concentration of at least 100 mg/ml, and a viscosity of 5-15 cP. *Id.* at 289. The applicant explained how these “interrelated factors”—“protein concentration, injection volume[,], and viscosity”—present serious “challenge[s].” *Id.* at 295-96. Excessive injection volume “risks damaging increases in intraocular pressure,” but lower volumes require a “relatively high” concentration “[i]n order to inject the target amount of VEGF receptor fusion protein (8 mg).” *Id.* Yet higher concentrations can increase viscosity, which may cause “damaging shearing forces to the protein and difficulty for the clinician who delivers the injection.” *Id.* The applicant then explained how, “[i]n spite of being constrained by these factors,” the

inventors “successfully developed several formulations that meet these criteria,” such as the “formulations including a variety of excipients” in Figures 3B, 3C, and 5 that “were measured to be within the 5-15 cP range specified in the claims.” *Id.* at 296. Thus, “a representative number of species encompassed by the claims have been disclosed.” *Id.* The Examiner withdrew the rejection “in view of Applicant’s amendment” and “persuasive arguments,” and allowed the claims. *Id.* at 308.

The references that Regeneron disclosed to the Examiner during prosecution included Vitti (Ex.1007), Furfine (Ex.1005), Dix (Ex.1006), Fiedler (Ex.1011)—each of which Alvotech relies on for its obviousness grounds—as well as Fiedler ’126 (Ex.2002), the Australian Public Assessment Report for Aflibercept (Ex.2003, “AusPAR”), Borwankar (Ex.2004), and Whitaker (Ex.2005). Ex.2001 at 236-37, 240, 251, 324, 371, 396-97, 400, 411, 527. The Examiner considered these references and declined to reject the claims on anticipation or obviousness grounds.

III. The Director Should Deny Institution Under 35 U.S.C. § 325(d)

The Director should exercise his discretion to deny the Petition under 35 U.S.C. § 325(d). The two-part test set forth in *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH* considers: “(1) whether the same or substantially the same art ... or substantially the same arguments previously were presented to the Office,” and, if so, “(2) ... whether the petitioner has demonstrated that the Office erred in a manner material to ... patentability.” IPR2019-01469, Paper 6, at 8

(P.T.A.B. Feb. 13, 2020) (precedential). “[T]he *Becton, Dickinson* factors provide useful insight” into the test and include, *inter alia*, “the similarities and material differences between the asserted art and the prior art involved during examination,” whether “the asserted art” is “cumulative” of “the prior art evaluated during examination,” “the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art,” and “whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art.” *Id.* at 9 n.10 (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (P.T.A.B. Dec. 15, 2017)).

“Challenging the claims using the same prior art that was previously presented on an IDS is sufficient to satisfy the first part of the *Advanced Bionics* framework.” *Ecto World LLC v. RAI Strategic Holdings Inc.*, IPR2024-01280, Paper 13, at 4 (P.T.A.B. May 19, 2025) (precedential). So too is raising “substantially the same arguments” advanced by the Examiner during prosecution. *Weatherford U.S., L.P. v. Enventure Glob. Tech., Inc.*, IPR2020-01661, 2021 WL 1432974, at *13-14 (P.T.A.B. Apr. 15, 2021). Thereafter, “a petitioner must explain how the Examiner erred” and “must provide an analysis [regarding error] even when the asserted prior art is on an IDS, but the Examiner did not apply the reference.” *Ecto World*, IPR2024-01280, Paper 13, at 5. And where the Examiner has “specifically” considered the same or substantially similar art or arguments, establishing material

error requires a showing “that no reasonable examiner could have found” the claims patentable. *Id.* at 6. “If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics*, IPR2019-01469, Paper 6, at 9.

Alvotech’s Petition raises five grounds—four asserting obviousness, and one challenging written description. Pet. 10. Alvotech’s obviousness grounds rely exclusively on references that are identical to, or substantially similar to and cumulative over, art considered during prosecution; and its written-description ground raises the same argument the Examiner considered and rejected during prosecution. Because Alvotech has failed to show material error as to either obviousness or written description, the Director should deny institution.

A. Alvotech’s Obviousness Grounds

1. Alvotech’s References Were Considered During Prosecution or Are Substantially Similar to Considered References.

Grounds 1, 2, 4, and 5 allege obviousness based on various combinations of Vitti (Ex.1007), AU Eylea Label (Ex.1009), Larson (Ex.1010), Furfine (Ex.1005), Dix (Ex.1006), Fiedler (Ex.1011), and 2011 Eylea Clinical Review (Ex.1008). Pet. 10. Each of those references was disclosed to the Examiner during prosecution on an IDS or is substantially similar to art that was disclosed. The first part of *Advanced Bionics*’s framework is thus satisfied. *Ecto World*, IPR2024-01280, Paper 13, at 4.

Vitti, Furfine, and Dix. Vitti, Furfine, and Dix all were disclosed repeatedly

on an IDS and considered by the Examiner. Ex.2001 at 240, 400 (citing Vitti, no. 121), 236, 324, 396 (Furfine, no. 064), 237, 397 (Dix, no. 075). The Examiner considered each reference. On each occasion, he wrote that “all references were considered except where lined through”; did not draw a line through Vitti, Furfine, or Dix; and applied his signature. *Id.* at 236-37, 240, 324, 396-97, 400. “Because [these references] were provided on the applicant’s IDS, ... the references were previously presented to the Office.” *Ecto World*, IPR2024-01280, Paper 13, at 4.

Fiedler. Fiedler both was presented to the Office and is cumulative over another reference that was disclosed to and considered by the Examiner. First, Fiedler is incorporated by reference on the face of the ’036 patent, Ex.1001, 32:61-64, as Alvotech acknowledges, Pet. 19. Fiedler’s incorporation by reference is sufficient for it to have been previously presented to the Office. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (“Incorporation by reference [means] ... that the material is effectively part of the host document as if it were explicitly contained therein.”).

Second, Alvotech’s Fiedler reference is substantially similar to and cumulative over another Fiedler reference, Fiedler ’126, that was considered by the Examiner. Fiedler ’126 repeatedly was disclosed to the Examiner on IDSs, and the Examiner confirmed that he considered it and applied his signature. Ex.2001 at 240, 400 (no. 124). Alvotech cites Fiedler as purportedly disclosing: (1) “a plastic pre-

filled syringe containing a VEGF antagonist” in “a liquid formulation” and “specifically identif[ying] EYLEA (aflibercept)”; (2) that “preferable volumes for intravitreal injections to a patient are 30 to 100 μ L,” including “a most preferable volume” of “0.05 ml”; (3) that “VEGF antagonist concentration is between 1 to 100 mg/ml”; (4) “that its formulations are administered intravitreally” without ever “specify[ing] a desired viscosity”; and (5) “the treatment of several intraocular neovascular (i.e., angiogenic) diseases,” including wet AMD, DME, and DR. Pet. 52, 56-57, 61-62, 65, 66-67. The same or nearly identical disclosures are present in Fiedler ’126. Ex.2002, ¶ 17 (“[T]he present invention provides a pre-filled syringe containing a liquid formulation of a VEGF antagonist ...”), ¶¶ 19, 74 (“more preferably the anti-VEGF antagonist is ... aflibercept,” and aflibercept “is presently marketed under the name Eylea”), ¶ 30 (“Preferably, a volume of 30 to 100 μ l of the liquid formulation is administered.”), ¶ 68 (“most preferably the volume ... is 0.05 ml”), ¶ 20 (“Preferably, the antagonist concentration is 1 to 100 mg/ml.”), ¶ 88 (“Preferably, the pre-filled syringe is for use in the intravitreal injection of a VEGF antagonist ...”), ¶ 29 (“preferably having an ocular disease selected from” AMD, DME, and DR). Fiedler thus is substantially similar to and cumulative over Fiedler ’126, which was considered by the Examiner during prosecution.

AU Eylea Label. The AU Eylea Label is cumulative to another reference that was disclosed to and considered by the Examiner during prosecution. Alvotech cites

AU Eylea Label as disclosing “generally well tolerated” “overdoses” of 8 mg; 30-gauge needles; treatment of angiogenic eye disorders via intravitreal injection of aflibercept; injection volumes of 50 μ L; maintenance or reduction of central retinal thickness; and maintenance of visual acuity as measured under the BCVA test. Pet. 22, 25, 28, 30-31, 38-42, 51-52, 54-58, 60, 65-66, 70-71, 86-88. But the Examiner considered AusPAR, a substantially similar Australian reference concerning the clinical development of Eylea. AusPAR was cited to and considered by the Examiner on an IDS during prosecution, Ex.2001 at 371 (no. 560), and contains the entire Australian Eylea Label as of July 2012. Ex.2003 at 94-112. AusPAR thus includes identical or substantially similar disclosures to the AU Eylea Label, including essentially verbatim passages relied upon in the Petition. *E.g., id.* at 111 (identically disclosing “isolated cases of overdoses with 8 mg”), 7 (“the syringe, when equipped with a 30 gauge, 0.5 inch needle, can deliver a single 50 μ L injectable dose containing 2 mg aflibercept”), 96 (“solution for intravitreal injection”), 97 (discussing studies showing “mean decreases in retinal thickness”), 98-99 (clinical studies found 95.33% of patients maintained visual acuity under BCVA), 101 (wet AMD indication). Thus, AU Eylea Label is substantially similar to and cumulative over AusPAR, which was previously presented to and considered by the Office.

2011 Eylea Clinical Review. This reference also is cumulative to a reference disclosed to and considered by the Examiner. Alvotech cites 2011 Eylea Clinical

Review for its purported disclosure of an absence of increase in blood pressure following intravitreal administration of Eylea. Pet. 87-89. But AusPAR, discussed above, contains substantively identical disclosures. Ex.2003 at 52 (“There was no clinically significant change in mean blood pressure values” in “Study VGFT-OD-0508[.]”); *id.* at 17, 27, 66 (similar). 2011 Eylea Clinical Review thus is substantially similar to and cumulative over AusPAR, which was considered by the Examiner.

Larson. Larson likewise is cumulative over references disclosed to and considered by the Examiner during prosecution. The Petition “is relying on Larson for [its] broad teaching” “of target viscosities for injected high-concentration protein formulations.” Pet. 18. Although it acknowledges that “Larson’s patent is directed to a specific way of reducing viscosity,” *i.e.*, through “using organic dyes,” the Petition brushes aside this specific teaching and asserts instead that “a POSA would have been well aware of other ways” to reduce viscosity. Pet. 18, 26. In other words, Alvotech ignores Larson’s disclosure of how to achieve low-viscosity formulations and instead relies on its teaching, in isolation, that ““less than or about 20 cP, or most preferably less than or about 10 cP”” viscosity was desirable for “formulations containing ‘greater than 100 mg/mL’ protein.” Pet. 23 (quoting Ex.1010, ¶¶ 75, 77, 167, 231); *see* Pet. 33-36, 52-53 (“target viscosity ranges”), 62-63.

The Examiner considered art that, like Larson, generically identifies viscosities of less than 20 cP or 10 cP for high-concentration protein formulations

(without teaching how to achieve such viscosities with aflibercept). For example, both Whitaker and Borwankar were submitted on an IDS and expressly considered by the Examiner. Ex.2001 at 251, 411 (Whitaker, no. 089), 527 (Borwankar, no. 655). Whitaker discloses “[a]cceptable’ (≤ 20 cP) and ‘preferred’ (≤ 10 cP) viscosity ranges” (identical to the Larson ranges on which the Petition relies) for “high (50 and 150 mg/mL), and ultra-high (175 mg/mL) protein concentration formulations.” Ex.2005 at 3, 6. Whitaker’s “[s]olution viscosities were measured at 25°C,” *id.* at 2, so it also teaches “viscosity ranges” “approximately equivalent to less than or about 22.52 cP, or less than about 11.26 cP at 20°C,” Pet. 64.

Similarly, Borwankar teaches that “the desired level of [viscosity is] 20 cP”—“measured[] after temperature normalization to 25 °C”—for protein formulations with “high concentrations (150 to 300 mg/mL).” Ex.2004 at 1, 3; *see also* Ex.2006 (Borwankar SI) at 5-6 (identifying formulations with protein concentrations of 69-149 mg/ml and viscosities of 3-12 cP at 25°C). Again, Borwankar’s desired viscosity range of 20 cP or less at 25°C is “approximately equivalent to less than or about 22.52 cP ... at 20°C,” just like Larson’s. Pet. 64.

Larson’s purported disclosure of desired viscosity ranges for high-concentration protein formulations thus is substantially similar to and cumulative of

the Whitaker/Borwankar disclosures the Examiner considered during prosecution.¹

2. Alvotech Has Failed To Show Material Error

Because all of Alvotech's references either were cited to the Examiner on IDSs, or are substantially similar to and cumulative over such references, the first part of the *Advanced Bionics* framework is satisfied. *Ecto World*, IPR2024-01280, Paper 13, at 5. And because Alvotech shows no material error in the Examiner's consideration of these references, the second prong of *Advanced Bionics* also is met.

Alvotech makes no argument that the Examiner misunderstood these references or somehow erred in his consideration of them, and thus cannot establish that the Examiner materially erred by not rejecting the claims as obvious. During prosecution, the Examiner expressly considered Dix, Furfine, Fiedler, Fiedler '126, AusPAR, Barwankar, and Whitaker, each of which (as detailed above) discloses the

¹ Alvotech relies on Larson to a lesser extent for other limitations, but the relevant disclosures are also cumulative over art considered by the Examiner. For instance, Larson's purported disclosure of intravitreal administration of Eylea through 18-32 gauge needles (Pet. 25-26, 33-34, 54-55) is cumulative over, among others, AusPAR. *E.g.*, Ex.2003 at 7, 106 ("syringe ... with a 30 gauge, 0.5 inch needle, [for] ... 50 μ L injectable dose containing 2 mg aflibercept"). Alvotech concedes that Larson's disclosure of using L-histidine as a buffer is cumulative over Dix. Pet. 37 (citing Ex.1010, ¶ 8; Ex.1006 at 10:14-11:1, 19:37-42, 20:37-41). Larson thus is entirely cumulative over references the Examiner considered during prosecution.

same or substantially similar teachings as the references making up Alvotech's obviousness grounds. For its obviousness grounds (unlike written description, discussed *infra* III.B.2), Alvotech makes no attempt to show that the Examiner erred in his consideration of the aforementioned art, which is the same as or substantially similar to Alvotech's obviousness references. Material error requires more than the "mere[] assert[ion] that the Petition 'details how the references disclose every element of every claim,'" *Tanklogix, LLC v. Sitepro, Inc.*, IPR2025-00761, Paper 10, at 2 (P.T.A.B. Sept. 3, 2025) (citation omitted), but that is all that Alvotech has provided here. Because Alvotech has not sufficiently identified any error, much less a material error, the Director should deny institution as to grounds 1, 2, 4, and 5.

B. Alvotech's Written-Description Ground 3

Alvotech re-litigates the same written-description argument that the Examiner advanced and then expressly withdrew upon consideration of Regeneron's argument and amendment. Because Alvotech's Petition asserts the same arguments that were previously presented to the Patent Office and fails to make any showing of material error, the Director should exercise his discretion as to ground 3 as well.

1. Alvotech's Written-Description Argument Was Considered and Rejected During Prosecution

The written-description theory advanced in Alvotech's Petition is indistinguishable from the one the Examiner considered and ultimately found unavailing. *Supra* 3-5. Just as the Examiner rejected the claims for "recit[ing] a

high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein,” Ex.2001 at 231, Alvotech faults the claims for “failing to specify any components of the formulation,” Pet. 77, 82. Just like the Examiner, Ex.2001 at 231, Alvotech asserts invalidity because the claims allegedly are not limited to the “narrow group of formulations” shown by the specification to “achieve the claimed results,” *i.e.*, the recited concentration, volume, and viscosity values, Pet. 81. And just as the Examiner considered whether, as the applicant urged, a representative number of species have been disclosed, Ex.2001 at 296, 307, Alvotech now maintains that a representative number of species have not been disclosed, Pet. 80. Indeed, Alvotech concedes candidly that its theory is duplicative, acknowledging that “[t]he Examiner initially recognized the written description problem” its Petition purports to identify, while arguing that the Examiner “erroneously believed Regeneron overcame [that problem].” Pet. 81. Alvotech’s written-description argument thus was previously presented to, expressly considered, and ultimately rejected by the Patent Office.

So too was Alvotech’s no-buffer argument. Although Alvotech characterizes this theory as an additional reason why the ’036 patent’s claims lack adequate written description, *e.g.*, Pet. 83 (“The challenged claims *also* lack written description support because they do not require a buffer—a component the specification makes clear is required.” (emphasis added)), its no-buffer argument is subsumed by its

primary, rejected written-description argument: that the claims are invalid because they fail to adequately identify the “components of the formulation other than the VEGF fusion protein itself, including whether it contains *a buffer*, a surfactant, a viscosity-reducing agent, or a thermal stabilizer ... let alone the identity or concentration of any such component.” Pet. 77 (emphasis added); Pet. 77-78 (observing that species “that achieve the required viscosity ... contain a buffer”).

Moreover, although the Examiner initially indicated that the specification only adequately described formulations “with 5% sucrose, polysorbate, *a histidine based buffer*, and L-arginine,” Ex.2001 at 231 (emphasis added), the Examiner withdrew his rejection based on Regeneron’s arguments and amendment. *Id.* at 308. The Examiner thus appreciated the “buffer” component but nonetheless deemed the claims adequately described, notwithstanding that they do not recite a buffer or the other components the Examiner originally insisted were necessary. The Examiner could not have allowed the amended claims without determining that the claimed formulations were adequately described. MPEP §§ 2163, 2163.05 (9th ed. Rev. Jan. 2024). Because Alvotech’s no-buffer argument is the same as or substantially similar to an argument that previously was presented to the Office, the first part of the *Advanced Bionics* framework is satisfied as to ground 3.

2. Alvotech Has Failed To Show Material Error

Alvotech’s disagreement with the Examiner’s written-description finding is

insufficient to show material error. The Examiner agreed with the applicant that the claims were adequately described because (1) a representative number of species have been disclosed, and (2) the claims need not recite additional ingredients (such as a buffer) apart from the VEGF antagonist and its associated limitations. Ex.2001 at 231, 289, 296, 308. Although Alvotech disagrees and repeats the Examiner's withdrawn rejection (Pet. 80), mere disagreement with the Examiner's ultimate conclusion is insufficient to show "that no reasonable examiner could have found" the claims adequately described. *Ecto World*, IPR2024-01280, Paper 13, at 6.

Alvotech comes nowhere close to meeting the "no reasonable examiner" standard. The '036 patent identifies nine different formulations with a 155 mg/ml concentration that achieve a viscosity of 15 cP or less in Figure 3B, Ex.1001, 9:46-10:4, 38:47-54, Fig. 3B; over a dozen formulations with 10-140 mg/ml concentrations that achieve such viscosities in Figure 3C, *id.*, 10:5-8, 38:55-67, Fig. 3C; over a dozen formulations that achieve such viscosities in Figure 5, *id.*, 10:24-29, 42:17-22, Fig. 5; and twelve formulations with a 140 mg/ml concentration that achieve such viscosities in Figure 9, *id.*, 10:45-11:26, Fig. 9. In total, at least 31 formulations with 100 mg/ml or higher concentrations, and viscosities of less than 15 cP, are disclosed. *Id.*, 9:46-11:26, 38:47-67, 42:17-22, Figs. 3B, 3C, 5, 9. In deriding this extensive set of disclosed species as "highly similar to one another," Pet. 80, Alvotech ignores that these 31 formulations included over a dozen different

ingredients and multiple concentrations thereof, including viscosity reducers (*e.g.*, arginine, lysine, sodium chloride, magnesium chloride), buffers (*e.g.*, phosphate, histidine), thermal stabilizers (*e.g.*, sucrose), surfactants (*e.g.*, polysorbate 20), and counterions and amino acids (*e.g.*, sodium sulfate, sodium thiocyanate, sodium citrate, glycine, sodium aspartate, sodium glutamate). *Id.* These facts are in no way “similar to *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d[] 566 (D. Del. 2018),” *contra* Pet. 81, a case in which a district court determined that there was “only *a single embodiment* within the broad scope of the claims” for which a “detailed description” was provided, *Pernix*, 323 F. Supp. 3d at 624-25 (emphasis added). Here, a reasonable examiner clearly could have found that these several dozen formulations comprising numerous ingredients and concentrations are sufficiently diverse as to be representative species.

That the claims do not recite certain ingredients (such as a buffer) does not undermine the Examiner’s allowance of the claims. “A claim is not defective when it states fewer than all of the steps that may be performed in practice of an invention,” and the claims here thus did not need to list every component of the compositions that may be used in the claimed methods. *Smith & Nephew, Inc. v. Ethicon, Inc.*, 276 F.3d 1304, 1311 (Fed. Cir. 2001). And as discussed above, the specification describes numerous representative embodiments of appropriate compositions to be used in the claimed methods. That satisfies written description: “The specification

does not need to describe every conceivable and possible future embodiment of the invention,” but rather need only “provide[] an adequate description that in a definite way identifies the claimed invention in sufficient detail such that a [POSA] would understand that the inventor had made the invention at the time of filing.” *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 127 F.4th 896, 916 (Fed. Cir. 2025) (cleaned up); *see also Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). The numerous working examples and detailed description of appropriate ingredients easily satisfies written description, as the Examiner correctly found.

Finally, Alvotech suggests that claim 1 (which recites a protein concentration of at least 100 mg/ml) is invalid because the specification does not demonstrate possession of all possible concentrations above that limit. Pet. 79 (“no stated upper limit” and “***no examples*** of VEGF fusion protein concentrations above 155 mg/mL that achieve the required viscosity levels”). This position, however, cannot be reconciled with Alvotech’s own obviousness theory, according to which a POSA wishing to administer at least about 8 mg of aflibercept would not have used volumes higher than 100 μ L or lower than 50 μ L, such that suitable concentrations would have ranged from 80-160 mg/ml. Pet. 71. Alvotech cannot simultaneously assert that claim 1 lacks written description because the specification does not describe formulations with concentrations above 160 mg/ml while arguing that a POSA would have recognized an implicit upper limit of 160 mg/ml for an 8 mg dose and

acknowledging that the specification describes 155 mg/ml formulations. *E.g.*, *Regeneron*, 127 F.4th at 916 (“We have affirmed findings of adequate written description for ‘open-ended claims’ where the upper bound ‘would be limited by what a person skilled in the art would understand to be workable’ and where the patent’s specification adequately supported that range.”).

At bottom, Alvotech’s written-description argument amounts to little more than disagreement with the Examiner regarding the ’036 patent’s disclosure of a representative number of species. Here, the specification discloses several dozen formulations with the claimed viscosities and concentrations, and with a wide variety of ingredients and amounts. Written description therefore is satisfied. And even if “reasonable minds can disagree regarding the purported treatment of the [written-description] ... argument[], it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics*, IPR2019-01469, Paper 6, at 9. Regeneron thus respectfully submits that the Director should “defer to [the] previous Office evaluation[] of the evidence” and deny institution under § 325(d). *Id.*

IV. Conclusion

For the foregoing reasons, Regeneron respectfully requests that the Director exercise his discretion under 35 U.S.C. § 325(d) to deny institution.

Date: November 26, 2025

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CERTIFICATION OF PAGE LIMIT

The undersigned certifies that this Discretionary Denial Brief complies with the 20-page limit provided in Section II.C.iii of the Interim Director Discretionary Process guidance available at <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process>.

Date: November 26, 2025

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CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that on November 26, 2025, I caused true and correct copies of the following materials:

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