

Filed on behalf of: Celltrion, Inc.
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2025-00456
Patent No. 11,084,865

**PETITIONER'S OPPOSITION TO
PATENT OWNER'S DISCRETIONARY DENIAL BRIEF**

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I. INTRODUCTION

In its Discretionary Denial Brief (Paper 7, hereinafter “Brief” or “Br.”), Regeneron chiefly asserts that the Board should exercise its discretion to deny Celltrion’s Petition regarding U.S. Patent No. 11,084,865 (“US865”) because Celltrion’s priority challenge purportedly rehashes arguments considered and rejected by the West Virginia district court and the Court of Appeals for the Federal Circuit. This is not accurate. The anticipation and obviousness invalidity arguments in Celltrion’s Petition are different than those raised in the district court and Federal Circuit, which focused on obviousness-type double patenting over an already-expired Regeneron patent and did not challenge US865’s priority claim. Further, the district court proceeding against Celltrion was limited to a preliminary injunction (“PI”) motion, which (1) was based on a very limited preliminary evidentiary record, (2) allowed Celltrion only a single, cursory brief and no hearing, (3) was not a final adjudication of anything and does not bind the district court or the parties as to what may be argued once a full trial is scheduled and held.

Regeneron also self-servingly speculates that the district court is likely to expedite a trial to be held no later than March 2026. But despite that the mandates have now issued in all appeals of actions consolidated with the Celltrion action by the Judicial Panel on Multidistrict Litigation, the district court *has not yet even scheduled a status conference to set a discovery schedule*, much less set an

expedited date for trial. Moreover, Regeneron has insisted that any district court schedule must be a single consolidated one that applies to all present and possible future suits and PI proceedings involving *US865*, including against biosimilar applicants that have not even been sued yet. Regeneron's own position thus seeks to delay a full trial on the merits to a date uncertain. Regardless, Celltrion, in this brief, agrees not to raise before the district court any argument concerning *US865* that it raised or reasonably could have raised in its Petition (*Sotera* stipulation). If the Petition is instituted, Celltrion also agrees not to seek a district court trial date on *US865* that would occur before any final written decision is issued by the Board.

Regeneron also incorrectly asserts that the district court (and the Federal Circuit in its decision affirming the PI against Samsung Bioepis ("Samsung")) already decided the priority arguments presented in the Petition. As demonstrated below, the priority arguments made in the Petition are based on different arguments, evidence, facts, and precedent than the cursory written description argument made in opposition to the PI motion at the district court. That different evidence includes the testimony of Regeneron's own expert in a previous, successful IPR Petition (IPR2023-00462 ("*IPR462*")), wherein the cancelled claims of US Patent No. 10,464,992 ("*US992*") also contained the stability limitation of "wherein at least 98% [or 99%] of the VEGF antagonist is present in

native conformation following storage at 5° C. for two months [or 24 months] as measured by size exclusion chromatography,” which was not presented to the district court. That testimony established the unpredictability of the art and demonstrated that the *US865* disclosure fails to support the broad scope of the formulations of the claims challenged here.

Regeneron also ignores the multiple post-grant proceedings brought before the Board regarding similar patent claims to its Eylea formulation, in which *every* challenged claim was cancelled in a final written decision or disclaimed by Regeneron either before or after institution. *US865*, like *US992*, is part of a “thicket” of weak secondary patents intended to shield Regeneron’s Eylea product from biosimilar competition long past the expiration of its original patent protection for aflibercept. Every time a member of that thicket has been challenged at the Board, the Board has cancelled the claims or Regeneron has declined to defend them. For example, *IPR462* challenged *US992*, a member of the same patent family as *US865* that had claims of almost the same scope as those challenged in *US865*. After trial was instituted, rather than allow its expert to be deposed, Regeneron disclaimed all of the challenged claims and the PTAB entered adverse judgment against Regeneron.

Finally, other considerations, such as public and economic policy, weigh against the Board exercising its discretion. Thickets of nuisance patents like

US865, *US992* and their numerous family members inflict huge and unjustified additional healthcare costs on the public. The Board should thus decline to exercise its discretion to deny institution.

II. BACKGROUND

The claims of *US865* are drawn to ophthalmic formulations containing VEGF antagonists that encompass the VEGF antagonist aflibercept. VEGF antagonists treat various eye disorders such as age-related macular degeneration (wet AMD) through intravitreal injection. By inhibiting the activity of VEGF, aflibercept can reduce or reverse vision loss. The original patents Regeneron received for discovering aflibercept and its use as a VEGF inhibitor have long since expired.

A. Regeneron’s Purple Book Patents Covering Aflibercept

US865 is one of over 75 patents that Regeneron listed in the Purple Book as purportedly covering Regeneron’s Eylea product or biosimilar versions thereof. *US865* is the eleventh patent to issue from a common specification that Regeneron filed on June 16, 2006, almost 20 years ago. This “thicket” of continuation patents is generally directed to the same “stable” formulation of aflibercept, with only trivial variations between family members. Most of the patents in the thicket are subject to terminal disclaimers over earlier-filed patent families claiming similar formulations of VEGF antagonist. Below is a table showing claim 1 from *US865* and representative claims from patents in which the claims have already expired

due to Regeneron’s own terminal disclaimer or other disclaimer of the claims. The highlighted claim terms represent overlap between the challenged claims of *US865* and the expired and disclaimed claims, focusing on the three limitations that Regeneron has asserted are inventive and patentable¹: a 40 mg/ml concentration of VEGF antagonist, glycosylation of that antagonist, and the stability achieved by the formulation (i.e., “wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.”)

Priority Document & Patent No.	Filing Date/Expiration Date	Representative Claim(s)
<i>US865</i> (EX1001)		1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises: a vascular endothelial growth factor (VEGF) antagonist[,] an organic co-solvent, a buffer, and

¹ Based on Regeneron’s argument, the district court also found in its decision granting the PI that Celltrion had not shown that placing the formulation in a vial was likely unpatentable over placing it in a pre-filled syringe. EX2004, 62, 114-115. Although this finding is incorrect, that limitation is not at issue here since the prior art relied upon, US2007/0293432, which has the same specification as *US865*, discloses the use of both.

Priority Document & Patent No.	Filing Date/ Expiration Date	Representative Claim(s)
		a stabilizing agent, wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.
16/159,269 (EX1008), US10,464,992	10/12/2018/ Disclaimed /Adverse Judgement² Entered against Regeneron	1. A vial comprising: a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography. 2. The vial of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation. 3. The vial of claim 1, wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4. 4. The vial of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

² Under 37 CFR §42.73(d)(3), “A patent applicant or owner is precluded from taking action inconsistent with the adverse judgment.”

Priority Document & Patent No.	Filing Date/ Expiration Date	Representative Claim(s)
15/879,294 (EX1009), US10,400,025	01/24/2018/ 3/7/2021	8. A formulation suitable for intravitreal administration comprising: (a) 40 mg/mL of a fusion protein comprising amino acids 27-475 of SEQ ID NO:4; (b) 0.03% polysorbate 20; (c) 10 mM sodium phosphate buffer, pH 6.2; and (d) 5% sucrose.
14/330,096 (EX1011), US9,340,594 (claim 5 recites Regeneron's Eylea formulation)	07/14/2014/ 3/7/2021	1. A pre-filled syringe suitable for intravitreal administration comprising a 1 mL luer glass syringe fitted with a plunger and a stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) trap, which consists of (i) a receptor component consisting essentially of an immunoglobulin-like domain 2 of a first VEGF receptor and an immunoglobulin-like domain 3 of a second VEGF receptor, and (ii) a multimerizing component, wherein the stable ophthalmic formulation comprises: (a) 1-100 mg/ml a VEGF antagonist; (b) 0.01-5% of one or more organic co-solvent; (c) 5-40 mM of buffer; and (d) optionally comprising 1.0-7.5% of a stabilizing agent. 3. The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months. 4. The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4. 5. The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.
11/818,463 (EX1016), US7,608,261	06/14/2007/ 3/7/2021	1. An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising

Priority Document & Patent No.	Filing Date/ Expiration Date	Representative Claim(s)
		a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4; b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol; c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride; and, d) 5-40 mM of sodium phosphate buffer. 6. The ophthalmic formulation of claim 1, comprising 10-80 mg/ml VEGF antagonist, 10 mM sodium phosphate, 0.03% polysorbate, and 135 mM sodium chloride, pH about 6.2-6.3. 7. The ophthalmic formulation of claim 6, comprising VEGF antagonist at a concentration selected from the group consisting of 10 mg/ml, 20 mg/ml, 40 mg/ml, and 80 mg/ml.

B. Previous Post Grant Proceedings Have Resulted in Cancellation of All Challenged Claims

Many of the Purple Book-listed members of Regeneron's patent thicket have been challenged before the Board and all have fared poorly. In fact, ALL challenged claims were either found unpatentable by the Board or disclaimed by Regeneron before or after institution. *See* IPR2023-00462, Paper 37 (adverse judgment on parent patent U.S. 10,464,992); IPR2023-00884, Paper 69 (adverse judgment on U.S. 11,253,572); IPR2023-00739, Paper 57 (adverse judgment on U.S. 10,888,601); IPR2022-01226, Paper 101 (all challenged claims of U.S. 10,888,601 unpatentable); PGR2021-00117, Paper 16 (disclaiming all claims of U.S. 10,857,231); IPR2023-00099, Paper 10 (disclaiming all claims of U.S.

10,857,205); IPR2023-00620, Paper 9 (disclaiming challenged claims of U.S. 10,406,226); IPR2023-00442, Paper 55, and IPR2022-01225, Paper 96 (all challenged claims of U.S. 10,130,681 unpatentable); IPR2022-00257, Paper 11, and IPR2021-00880, Paper 89 (all challenged claims of U.S. 9,669,069 unpatentable); IPR2021-00881, Paper 94 (all challenged claims of U.S. 9,254,338 unpatentable).

Celltrion itself previously brought seven IPR petitions (including joinder petitions) and one PGR petition against Regeneron's Purple Book-listed patents. All of those resulted in the cancellation of all challenged claims. In one IPR and the PGR, Regeneron disclaimed the claims before the Board even had an opportunity to decide institution. As discussed above, in *IPR462* (challenging *US992*, which has the same specification as *US865*) the challenged claims were almost the same scope as those challenged in *US865*, e.g., they included the same stability limitation, and the Board instituted. Section II.A. *US992*, however, while claiming that the VEGF antagonist is made in CHO cells, did not explicitly claim that the VEGF antagonist is glycosylated. Nevertheless, it is undisputed that a POSA would have understood that producing the VEGF antagonist in CHO cells, the only method of producing VEGF antagonist disclosed in the common specification, would naturally result in glycosylation. *See* Pet., 49-50; EX2005, 24-25. Regeneron conveniently disclaimed the challenged claims before

deposition of its expert and adverse judgment was entered against it. IPR2023-00462, Paper 37; *see* 37 CFR §42.73(d)(3) (“A patent applicant or owner is precluded from taking action inconsistent with the adverse judgment.”).

In view of Regeneron’s track record of conceding the invalidity of similar claims challenged in multiple Petitions filed prior to its suit against Celltrion, Regeneron’s argument that the instant Petition should be denied because of how long Celltrion waited to file its Petition after the district court complaint had been filed (but not served) does not support discretionary denial. Celltrion, which has labored hard to use the IPR process to clear key members of Regeneron’s Eylea patent thicket prior to district court litigation, had no way of knowing which of the many Purple Book-listed patents Regeneron would actually assert. Even when Regeneron filed its complaint, it initially asserted that Celltrion’s aBLA infringed 38 of its patents. Celltrion also could not know which of those patents Regeneron would assert in the PI proceeding. And Celltrion had already succeeded in obtaining adverse judgment against *US992*, which, as discussed above, has claims of very similar scope as *US865*, making its choice by Regeneron seem less likely. EX1053.

Regeneron also asserts that because Celltrion filed its Petition fourteen months after the complaint was filed, the Petition was statutorily time barred under 35 USC §315(b). Regeneron relies on *GoPro, Inc. v. 360Heros, Inc.*, IPR2018-

01754, Paper 38, 9, for this assertion. But Regeneron's reliance is misplaced. That Board decision actually stands for the proposition that "if service of a pleading asserting infringement occurred 'in a manner prescribed by law,' then *the one-year time period for a petitioner to file a petition under § 315(b) is triggered on the date of service.*" *Id.*, 10 (emphasis added). The date from which one determines whether a petition is time-barred is the date the complaint was served, not filed. As Celltrion noted in its Petition, the complaint was not served until October 16, 2024. Pet., 17-18; EX1050; EX1051, 10; EX1052, 2. Celltrion's Petition was filed within three months of the service date, and is thus not time-barred.

Given the number of related patents that the Board has cancelled, and Regeneron's attempt to prevent biosimilar entry by asserting a patent with claims having similar scope to those canceled claims and claims that Regeneron disclaimed, the Board should decline to exercise its discretion to deny institution. Furthermore, Celltrion agrees not to raise before the district court any invalidity grounds it raised or reasonably could have raised in its petition challenging *US865* and also agrees not to seek a trial on *US865* that would occur before the Board issues its final written decision. Thus, the timing of Celltrion's petition weighs against denial. *See* IPR 2020-00019 (*Fintiv*), Paper 11, 11 (recognizing that it is reasonable for a petitioner to wait to file its petition until it learns which claims are being asserted against it in a parallel proceeding).

III. CELLTRION’S PRIORITY ARGUMENTS ARE NOT THE SAME AS THE WRITTEN DESCRIPTION ARGUMENTS IN THE PARALLEL PROCEEDINGS

Regeneron spends a significant portion of its brief arguing that Celltrion’s challenges here are “redolent” of arguments it made earlier in different proceedings. *See, e.g.*, Br., 2-5, 7-16, 22-32. Regeneron’s arguments mischaracterize the procedural posture of the district court and appellate proceedings and the arguments Celltrion advances here. Regeneron’s discussion of prior proceedings conspicuously omits the prior post-grant proceedings (both IPR and PGR). And while Regeneron uses a broad brush to characterize the written description invalidity challenge before the district court and the priority challenge of the instant Petition, the Petition raises different arguments, evidence, and precedent from those raised in the prior district court and Federal Circuit proceedings cited in Regeneron’s brief.

Regeneron essentially argues that once a challenger raises one written description argument, all other written description-related arguments, such as challenging the effective filing date of the challenged claims, have also been raised. This faulty logic is analogous to arguing that any anticipation argument or any obviousness argument is the same as any other. Regeneron offers no case law supporting such a proposition, and in fact the applicable law compels the opposite conclusion. *Cf. Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (“each case must be decided on its own facts” (citation omitted)); *Biogen Int’l*

GMBH v. Mylan Pharmaceuticals Inc., 18 F.4th 1333, 1342 (Fed. Cir. 2021)

(noting that written description depends on the nature of the invention and is highly dependent on the facts of each case).

As explained below, the priority arguments in Celltrion’s Petition made in support of its anticipation and obviousness arguments are different from, and do not include, the written description arguments raised in the district court in the PI proceeding and *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.*, 1:22-CV-61 (N.D.W.Va.) (“*Mylan* trial”).

A. Preliminary Injunction Proceedings

Regeneron’s argument that Celltrion’s petition falls afoul of “[f]our decisions of the Northern District of West Virginia and *two* decisions of the Court of Appeals for the Federal Circuit,” (Br., 1 (emphasis in original)) is not correct.

As an initial matter, Celltrion is indisputably only a party to its own BPCIA litigation in West Virginia. The *Mylan* trial that Regeneron cites took place before Celltrion was even sued. Celltrion had no opportunity to participate in that proceeding much less examine witnesses or present its own evidence. Moreover, the PI proceedings against Formycon and Samsung are distinct from Celltrion’s. While Celltrion, Formycon, and Samsung shared an invalidity expert, the arguments each party raised in their separate oppositions to Regeneron’s separate, serial PI motions were distinct. Indeed, separate decisions were rendered on

Celltrion's arguments at both the district court and on appeal. *E.g.*, EX2002-EX2007. Regeneron has no basis to lump together all of these distinct parties and proceedings.

Further, although the district court issued a preliminary order granting Regeneron's motion for a PI in the Celltrion action, that order was based on a very preliminary and incomplete record, as the Federal Circuit acknowledged. *See* EX2007, 9-10. The discovery exchanged as part of the PI proceeding consisted of a limited document production by both sides and depositions of just those who submitted declarations. Celltrion's only opportunity to address Regeneron's motion was a 25-page opposition brief that had to address both *US865* and U.S. Patent No. 11,793,926 ("*US926*"), a patent on plastic packaging for syringes that Regeneron would later drop, as well as economic issues, such as irreparable harm and nexus.³ *See* EX2012, 17-19. Accordingly, Celltrion had to significantly truncate its invalidity arguments.

The totality of Celltrion's PI briefing on written description was the following single paragraph:

³ Celltrion also submitted a three-page sur-reply in response to Regeneron relying on new evidence as to anticipation and obviousness in its reply, which Regeneron sought to exclude.

The Asserted Claims are invalid for lack of written description under 35 U.S.C. § 112 because a POSA would not have understood the inventors to be in possession of the claimed “native conformation” range of 98%-100%. For there to be written support, “a skilled artisan must be able to reasonably discern a disclosure of that range.”

Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1328 (Fed. Cir. 2021). Here, the specification does not describe that range and the % native conformation data in the examples ends at 99.2%, not 100%. Tessier ¶¶338-61. Because the upper part of the claimed range is nowhere found in the specification and achieving 100% stability can be difficult, a POSA would not have understood the inventors to be in possession of it. *See also Columbia Ins. Co. v. Simpson Strong-Tie Co.*, No. 2021-2145, 2023 WL 2733427, at *4-5 (Fed. Cir. Mar. 31, 2023) (insufficient written description where claims recited a range but specification disclosed only lower bound of the range and no upper limit).

EX2012, 16-17 (footnote omitted). Celltrion’s arguments were thus very brief and preliminary, and do not limit further written description arguments that it may make at the district court during the full trial (yet to be scheduled), and thus should not limit such arguments in Celltrion’s IPR Petition. *See* EX2007, 10 (noting that

“Celltrion will have the opportunity to fully develop” defenses during a full trial on the merits).

The preliminary written description argument made to the district court was also very different than the priority challenge in the Petition and is not repeated in the Petition. Pet. 26-47. In the PI proceedings, Celltrion challenged the sufficiency of the '865 patent's written description under 35 U.S.C. § 112, first paragraph based on the difficulty a POSA would have experienced in achieving a formulation that was 100% stable over time. *See* EX2012, 16-17. In contrast, the challenges in this IPR concern the effective filing date of *US865*, an issue not raised by Celltrion (or any other defendant) in the district court, or at the Federal Circuit. Pet., 26-47. This effective filing date challenge also relies on (a) different evidence, including testimony of Regeneron's own expert directly related to why a POSA would not understand that the inventors invented what is now claimed in *US865* before October 12, 2018, and (b) different legal precedent. *Id.*

The priority challenge is based in part on the fact that the examples, which are the only part of the specification relied upon by Regeneron to support the stability limitation, do not support the broad challenged claims. Pet. 36-37, 38-40. This priority challenge is fully supported by Regeneron's expert, Dr. Klibanov, who testified in *IPR492*, challenging *US992*, whose claims recite the same stability limitation. More specifically, Dr. Klibanov testified that the art is unpredictable

and there is no way of knowing how stability will be affected by changing excipients such as the buffer.

The challenge also relies on the Tables of the Examples “% VEGF Trap Recovered” reported in each example of *US865*. As explained in the Petition, the % VEGF Trap Recovered, which Regeneron takes to refer to the amount of non-aggregated aflibercept still in the sample at a particular time, is measured the same way—size exclusion chromatography—as % VEGF Trap Native Configuration, which, Regeneron relies upon to support the added stability limitations. Pet., 42-44. As discussed in the Petition, % VEGF Trap Recovered has fluctuations showing that the measurement errors may be as high as 13%. *Id.*, 44. Because of those measurement errors, a POSA would not have understood that the examples relied upon by Regeneron provide written description support for the added stability limitation. *Id.*, 42-45.

Not only are Celltrion’s arguments made in the Petition different from those made in its opposition to Regeneron’s PI motion, Celltrion’s Petition also highlighted an admission that Regeneron made during Samsung’s Federal Circuit appeal of the PI decision against it, wherein Regeneron argued that the only information provided by the *US865* examples is insufficient to obtain the claimed stability and that the stability of the same formulation disclosed in those examples can vary from lot-to-lot. In particular, Regeneron argued with respect to claim 5 of

US594, a claim that has the same excipients as *US865* (and *US992*) Examples 3 and 4 (the Eylea formulation), that “claim 5 [of *US594*] (unlike Example 3) is not directed to a particular lot of aflibercept...; accordingly, the formulations of claim 5 do not always achieve the 98% native conformation after 2 months achieved in Example 3 [of *US865*] and required by the asserted claims, foreclosing a finding of inherency.” EX1048, 50; Pet., 36.

Also, while the district court found that, on that brief and preliminary record, Celltrion had not shown a substantial question of invalidity on the written description question Celltrion presented, Celltrion has not yet had a full opportunity to develop that defense at the district court. *See* EX2007, 10. And because Celltrion was not able to sufficiently develop the written description challenge given the preliminary nature of the proceeding and paucity of briefing allowed, Celltrion understandably chose not to appeal the district court’s preliminary findings as to written description.

B. Mylan District Court Proceeding

Regeneron argues repeatedly that “across four decisions—one 313-page bench-trial decision, and three ~200-page decisions granting preliminary injunctions, Ex.2001-2004—the District Court upheld the ’865 patent against every validity challenge the defendants could conjure, including written-description challenges redolent of Celltrion’s priority-based argument here.” Br. 2, *see also*

id., 1, 3, 4, 19-20, 35-36. Most of those decisions relied upon by Regeneron were issued in proceedings to which Celltrion was not a party, and Regeneron does not, and cannot, controvert that Celltrion has only been allowed, at most, 28 pages of briefing, only a single paragraph of which pertained to written description.

Mylan's written description argument before the West Virginia district court was also different than the priority challenge in Celltrion's Petition. Mylan's argument was based on the allegation that the claims recited the structural categories of "buffer" and "stabilizing agent" instead of specific chemical structures, and thus did not support the full scope of the claims. EX2001, 210-217. In contrast, as discussed in Section III.A., Celltrion's Petition makes the entirely new argument that given the possible error introduced using size exclusion chromatography, a POSA would not understand that the data reported for "% VEGF Native Confirmation" in the Tables provided written description support for the claimed stability. Pet., 42-44.

The district court's finding against Mylan was also based on the evidentiary record in that case. At the *Mylan* trial, Regeneron's expert, Dr. Trout, testified that the components of the claimed formulation of *US865* "have 'common structural features,' including the 'very specific' VEGF antagonist and the categories of organic cosolvent buffer, and stabilizing agent," whose structures were well known

in the art. *Id.*, 211. Based on the specific evidence presented at trial in *Mylan*, the district court found:

the evidence demonstrated that the examples in the specification were predictive of the performance of formulations that were not exemplified in the patent. Regeneron pointed to several working examples of embodiments that were outside the disclosed examples (and the prior art) but nonetheless met the 98% native conformation and turbidity limitations of the claims.

Id., 214.

The evidence in Celltrion's Petition is different than what was presented in *Mylan*. For example, the Petition points out that Regeneron has made arguments to the Board that directly contradict the above evidence and findings of the district court in *Mylan*. Regeneron, in *IPR462*, submitted the testimony of its expert Dr. Klivanov opining that the art is unpredictable. Pet., 40-41. Dr. Klivanov testified that factors beyond "buffers" and "stabilizing agents" can affect stability including glycosylation, excipients, and protein concentration, further testifying that "it was known that even a minor change in any of the aforementioned variables could affect whether a protein remains in its native conformation over time," and that "the magnitude of the effect would be impossible to predict based on theory alone." EX1021 ¶50; Pet., 41. That testimony is especially relevant

given the narrow range of formulations Regeneron tests in its examples. Pet., 38; see Section III.C.1. That testimony also directly contradicts the evidence relied upon by the *Mylan* district court, including the testimony of Dr. Trout. Despite Dr. Klibanov's contradictory testimony to the Board, neither Mylan nor Regeneron presented this evidence to the district court. Pet., 26-47.

In its Petition, Celltrion also highlights Regeneron's admission from Samsung's appeal of the PI decision against it to the Federal Circuit that the information provided by the *US865* examples is insufficient to obtain the claimed stability and that the stability of the same formulation disclosed in those examples can vary from lot-to-lot.

Another difference between Celltrion's arguments in the petition and Mylan's district court arguments is that Mylan only challenged the validity of claims 4, 7, 9, 11, and 14-17, while Celltrion's petition challenges claims 1-50 of *US865*. Claim 1 is much broader in scope than claim 4 and unquestionably lacks written description support. Moreover, since Regeneron is limited to asserting only claims 4, 7, 9, 11, and 14-17 against Celltrion during a full trial, the district court will not consider the patentability of most of the claims challenged in the Petition. Regardless, a settlement between Mylan and Regeneron following oral argument at the Federal Circuit resulted in the district court's decision in the *Mylan* trial being vacated and dismissed with prejudice. EX1054, 2. Thus, the district

court's decision in the *Mylan* trial is both unreviewable by the Federal Circuit and not binding on any party, particularly a non-party such as Celltrion.

C. This IPR Discusses Issues, Provides Evidence, and Relies on Evidence That Was Not Before the District Court or Federal Circuit

Regeneron provides a Table in its Brief where it cherry-picks isolated sentences from the Petition and from all the district court and Federal Circuit decisions. Br. 7-16. Regeneron conveniently fails to address in that Table the arguments presented for the first time in the Petition, examples of which are provided above in Sections III.A and III.B. For example, in the first row, Regeneron cites the Petition at 2-3 (part of the Introduction), which discusses the breadth of the claims. Regeneron then cites the district court's decision from the *Mylan* trial, to which Celltrion was not a party. In citing that decision, Regeneron declines to address its own evidence that it presented to the PTAB in *IPR462*. Regeneron also ignores the argument it made to the Federal Circuit in its opposition to Samsung's appeal of the PI decision that Example 3 is not limited to a particular lot of the formulation, and thus the claimed stability purportedly could not be inherent in the formulation tested in that Example. That is important, since *US865* provides no guidance beyond the excipients/formulation used in the examples as to additional factors that would influence the stability of the formulation for two months or twenty-four months. Pet., 32-35. The remainder of

Regeneron's arguments in the Table suffer from similar failings. Regeneron also fails to mention that every claim challenged at the PTAB in related patents has been cancelled, including claims containing the same stability limitation as the US865 claims. *See* Section II.B. Regeneron should not be rewarded for presenting different and conflicting arguments in different proceedings as to the validity of its patent claims. *Cf. Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003) ("It is axiomatic that claims are construed the same way for both invalidity and infringement.").

Besides failing to acknowledge its own admission before the Federal Circuit and the evidence of its own experts, as discussed below, in arguing that the issues significantly overlap between the district court and appellate proceedings and the instant Petition, Regeneron also fails to acknowledge the additional precedent that was not cited to the district court or the Federal Circuit due to briefing constraints and the preliminary nature of the proceedings.

1. The Native Conformation (Stability) Limitations

Celltrion argues in the Petition that the disclosure fails to provide written description support for the added stability limitations. Pet., 32-45. In doing so, Celltrion cites precedent, such as *Regents of the Univ. Minn. v. Gilead Sciences Inc.*, 61 F.4th 1350 (Fed. Cir. 2023) for lack of blaze marks and *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320 (Fed. Cir. 2000) to support arguments

regarding Regeneron's over-reaching in the claims. The district court did not cite or acknowledge this law in granting Regeneron's motion for a PI against Celltrion.

According to Regeneron, the district court found in the PI proceedings, and the Federal Circuit affirmed in the Samsung appellate decision, that the specification adequately describes the stability limitations because *US865* purportedly contains multiple disclosures of native conformations between 98% and 100%. Br. 26. While the district court may have found that "no cobbling together of numbers is necessary—the '865 patent contains multiple disclosures of native conformations throughout the range of 98% to 100%," the only support for those limitations is the data provided in the tables of the examples. Br., 26; EX1048, 58-59, 61-62; EX1048, 7-8; *see also* EX2001, 212 (noting that Dr. Trout testified that "all of the Product Patent's examples have 'at least 98 percent native conformation as measured by SEC after two months,' and all 'meet the turbidity limitation of Claim 15.'"). The Petition points out the fatally-limited nature of those examples. Pet., 35-39. And notably, Regeneron never addresses the testimony of its own expert in *IPR462* (involving *US992*), in which the claims contained the same stability limitations at issue here. In *IPR462*, Regeneron's expert, Dr. Klibanov, testified that (1) the art was highly unpredictable, (2) even small structural differences between proteins can lead to significant stability differences, (3) other factors that can affect stability include glycosylation,

excipients, and protein concentration, and (4) it was known that even a minor change in any of the aforementioned variables could affect whether a protein remains in its native conformation over time.” Pet., 41. Regeneron disclaimed the claims of *US992* the day before Dr. Klibanov’s deposition and accepted adverse judgment rather than allow cross-examination of its expert on these admissions.

Celltrion’s Petition presents additional arguments as to why a POSA would not recognize that the inventors invented the challenged claims. Regeneron’s Brief fails to address those arguments. In particular, the tables of the examples not only contain data for “% VEGF Trap Native Configuration,” but also contained “% VEGF Recovered.” *E.g.*, Pet., 37. Given that both “% VEGF Trap Native Configuration” and “% VEGF Recovered” were measured the same way—by SEC—and given the large variability in the reported “% VEGF Recovered,” a POSA would read the data presented for “% VEGF Trap Native Configuration” as including a margin of error of at least 3-13%, which far exceeds the claimed 1-2% stability range. Pet., 42-44.

Regeneron argues further that the district court found that Dr. Tessier’s testimony there supported that the specification supported the 98-100% range. Br., 29. Again, the cursory argument and evidence presented in the PI motion was preliminary and necessarily limited given the nature of the motion and the lack of any hearing. More importantly, however, the written description arguments made

at the district court are simply not part of the arguments challenging priority made in the Petition. *See* Section III.A. And Celltrion's expert in this Petition, Dr. Tessier, relies on evidence that was not presented to the district court.

Accordingly, the arguments in the Petition as to the stability limitations do not substantially overlap with those made in the preliminary district court and appellate proceedings, and Regeneron's arguments to the contrary are disingenuous and do not support discretionary denial.

2. Construction of Stability Limitations

Regeneron also argues that Celltrion's construction of the stability limitations, *i.e.*, that "wherein at least 98% [or 99%] of the VEGF antagonist is present in native conformation following storage at 5° C. for two months [or 24 months] as measured by size exclusion chromatography," should be construed as a 2% [or 1%] change from the initial amount of VEGF antagonist at time 0, was rejected by the Federal Circuit. Br., 27-29. But that should not preclude institution of the petition because the Federal Circuit's view of claim construction was preliminary and there has been no claim construction briefing or *Markman* hearing even scheduled at the district court. The evidence cited in the Petition supports that a POSA would construe stability as looking at conformation over time, and not dictated by an initial purity. *See* Pet., 24-26; EX2004, 101 (district court acknowledging claims do not require an initial purity limitation). Indeed, the fact

that the Board would be the first tribunal to fully and finally consider the meaning of this disputed claim term weighs in favor of institution, not against. And as discussed in Section IV.E.2 and the Petition, US2007/0293432 (“*US432*”), the prior art Celltrion relies on in its anticipation and obviousness grounds, has the same disclosure as *US865*, and thus necessarily anticipates or renders obvious the challenged claims of *US865*, regardless of how the claims are construed. Pet., 26, 47-48.

3. Glycosylation Limitation

As the Petition notes, the *US865* specification only mentions glycosylation once, when disclosing a single glycosylated variant that is glycosylated at all five of the asparagine residues in aflibercept to which glycans may be attached. Pet., 45-46. Regeneron’s argument that the written description for glycosylation has been decided relies on findings in the Samsung appellate decision, to which Celltrion was not a party. Br., 30-32. Even if relevant, Samsung’s argument differs from Celltrion’s argument in the Petition. Samsung argued on appeal that the examples only disclosed “VEGF SEQ ID NO: 4,” which could cover “at least thirty possible forms of aflibercept,” including aflibercept that is not glycosylated. EX(1063), 47. In contrast, Celltrion’s argument is based on the fact that the specification only discloses one glycosylated variant. Pet., 45-46.

In fact, the quote from the Federal Circuit decision reproduced by Regeneron supports the Petition’s argument, as it acknowledges that the “’865 specification, in discussing the preparation of the VEGF trap, states that *the VEGF trap in a specific embodiment comprises amino acids 27-457 of SEQ ID NO:4, i.e., aflibercept, and is glycosylated at Asn residues 62, 94, 149, 222 and 308....*

Regeneron presented expert testimony that a relevant artisan reading those examples would look to the rest of the specification to see how the VEGF trap was made, would note the specification’s disclosure that glycosylation results from a particular method of manufacture, *and would understand the VEGF trap to be glycosylated at those specific residues.*” Br., 30-31 (emphasis added).

Thus, Regeneron’s arguments as to glycosylation do not support discretionary denial.

IV. THE BOARD SHOULD DECLINE TO EXERCISE ITS DISCRETION UNDER SECTION 314(A) TO DENY INSTITUTION⁴

A. Proximity of the Trial date to the PTAB’s Statutory Deadline (*Fintiv* Factor 2)

While Regeneron asserts that a different party, Samsung, has requested an expedited trial in March 2026, there has been no movement at the trial court.

⁴ Regeneron did not argue that the Board should exercise its discretion under 35 USC §325(d), thus Celltrion does not address it here.

Regeneron also fails to inform the Board that in the MDL proceeding, it insists on maintaining a “single coordinated proposed schedule” that takes into consideration any future “potential preliminary injunction proceedings,” including all biosimilar applicants who have not been sued yet but Regeneron may choose to sue. *See* EX1055, 1. At this time, Celltrion is not aware of all the possible parties Regeneron may target as part of those PI proceedings, much less how much time Regeneron will seek to add to the schedule to accommodate those proceedings and any full trial on the merits that must eventually occur after all PI motions are decided and their outcomes potentially appealed via the same kind of interlocutory appeals that have essentially stayed all of the district court actions to date.⁵

Moreover, Celltrion avers that it will not pursue an invalidity defense in the parallel litigations (Nos 23-cv-89 and 24-cv-53 (N.D.W.Va)) that the claims subject to the instituted IPR are invalid based on the grounds that were raised or any grounds it reasonably could have raised in this IPR. *See Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12. And if the Board institutes this IPR, Celltrion will not seek a district court trial date on *US865* scheduled prior to the

⁵ Celltrion recognizes that Regeneron has noted to the district court that Alvotech, a party that has not yet been sued, may become part of the MDL, but Regeneron also does not provide a response from the district court. EX1055.

date the Board issues its Final Written Decision. That, along with the *Sotera* stipulation, addresses any concerns regarding duplication of effort by the trial court and this Board, greatly favoring institution.⁶ *Id.*, 19. As Chief Judge Boalick’s memorandum makes clear, a timely filed *Sotera* stipulation remains “highly relevant.” March 24, 2025 *Fintiv* Guidance, 2-3.

B. Possibility of a Stay (*Fintiv* Factor 1)

The possibility of a stay has not been raised in the litigation against Celltrion. Without “specific evidence” of how the court would rule on any stay motion, this factor is neutral. *Sand Revolution II, LLC v. Continental Intermodal Grp. – Trucking LLC*, IPR2019-01393, Paper 24, 7 (informative).

Moreover, the district court has not set a status conference since the mandates issued in the Federal Circuit appeals, entered any schedule for fact or expert discovery or claim construction, and indeed discovery has not even been

⁶ Celltrion recognizes that the PTAB’s FAQ’s as to the new discretionary denial process recommends that any stipulations be filed as soon as possible. Celltrion’s Petition, however, was filed before Former Director Vidal’s memo addressing discretionary denial was rescinded, and before the new bifurcated proceedings were instituted. Celltrion believed, and still believes, that its unpatentability challenges are very strong.

opened (apart from the limited discovery exchanged as part of PI proceedings). Given Celltrion's assurance that it will not seek a district court trial date on *US865* scheduled prior to the date the Board issues its Final Written Decision, on balance of all considerations, this factor favors institution.

**C. Investments in Parallel Litigation and Extent of Overlap
(*Fintiv* Factors 3 and 4)**

Regeneron originally filed a district court case against Celltrion, asserting that Celltrion was infringing 38 patents. The number of patents was narrowed to two for its PI motion against Celltrion, *US865* and US11,793,926 ("*US926*"), which was further narrowed to only *US865* after Celltrion filed its 25-page opposition brief (thereby requiring Celltrion to address *US926* and curtailing Celltrion's briefing concerning *US865*). That 25-page brief not only addressed those two patents, but all four of the PI equitable factors.⁷

The district court required all parties to the PI to submit a proposed order. The district court then essentially adopted a nearly 200-page order proposed by Regeneron in granting the PI, which also heavily relied on findings from the 313-

⁷ Celltrion's three-page sur-reply addressing obviousness-type double patenting in view of new evidence submitted by Regeneron in its reply was also entered by the district court.

page decision in the *Mylan* trial involving different invalidity challenges that Celltrion never had the opportunity to address. Prior to granting the PI, the district court did not hold a hearing.

Moreover, in the litigation against Celltrion, the district court has yet to enter a schedule, and it is likely this IPR will conclude before the district court reaches a final verdict. In addition, Regeneron is asserting multiple patents against Celltrion, and it is unlikely that Regeneron will assert all 50 claims of *US865* that Celltrion is challenging here. And as discussed above in Section III.A, Regeneron's PI motion was exactly that, a preliminary proceeding. Not only has trial not been scheduled, discovery has not even been allowed to commence, and there has been no *Markman* hearing. The Federal Circuit decision is not binding on how the district court may decide the parties' claims and defenses at the full trial. *E.g.*, EX2007, 10. Thus, if trial is instituted and the challenged claims of *US865* determined unpatentable by the Board, it will preserve district court resources as it will not have to include it in any full trial on the merits. *See* Section IV.A (Celltrion presents a *Sotera* stipulation and also stipulates not to pursue trial on *US865* until a final written decision is issued by the Board).

1. District Court Proceedings

The district court's investment in the parallel litigation involving Celltrion, as well as Samsung and Formycon has been minimal. *See, e.g., Duke Mfg. Co. v.*

Low Temp Indus., Inc., IPR2021-00415, Paper 13, 13 (“Although we appreciate that the court and the parties have invested effort and time in the preliminary injunction proceedings, it remains that much work lies ahead despite the district court having granted the preliminary injunction.”). And as to the district court’s investment in the *Mylan* trial, as discussed in Sections III.B, and III.C, that trial involved different written description arguments. Moreover, given Regeneron’s settlement with Mylan prior to a judgment on Mylan’s appeal of the district court’s decision, it is unclear if the portion of the decision regarding written description would have survived. This factor thus favors institution.

Regeneron’s citation of *Fintiv* to support its contention that the district court had made substantial investment in the parallel litigation based on its deciding Regeneron’s motion for PI against Celltrion in which it addressed the validity of *US865* is disingenuous at best. *Fintiv* cites *E-One, Inc. v. Oshkosh Corp.*, IPR2019-00162, Paper 16 at 8, 13, and 20, to support its statement that “if, at the time of the institution decision, the district court has issued substantive orders related to the patent at issue in the petition, this fact favors denial.” *Fintiv*, 9-10, n.16. *Fintiv* itself does not mention a PI. In *E-One* (IPR2019-00162), the Board noted that the petition presented two grounds of patentability that had been advanced in the litigation. *Id.*, Paper 16, 13. Moreover, as the Board found in that IPR, the district court had received claim construction briefing, held a hearing on

the same, and issued a claim construction order. *Id.* None of those findings by the Board in IPR2019-00162 are present here. *See also Edwards Lifesciences Corp. v. Evalve, Inc.*, IPR2019-01479, Paper 7, 7-12 (noting in denying institution that, *inter alia*, trial would be concluded before the Board could issue a final written decision, that petitioner relied on substantially overlapping arguments in its petition and at the district court, and had a hearing on claim construction). As discussed above in Sections III.B and III.C, the invalidity grounds in Celltrion's Petition are very different from what was argued at the district court in the PI briefing. Furthermore, the district court has yet to set a trial schedule, and there has been no briefing or hearing on claim construction, much less a claim construction order. And as already discussed in Section III.B, the Petition addresses more claims than were addressed at the district court, with many of those claims being broader than those addressed by the district court. Also, since Regeneron and Mylan settled, the district court decision in the *Mylan* trial has been vacated.

2. Federal Circuit Appeals

Regeneron also asserts that there has been substantial investment in the appeals to the Federal Circuit. As noted in Section III.B, Regeneron settled with Mylan, so the Federal Circuit will not have to write a decision in that appeal. With regard to the appeals of the PI proceedings, as explained in Sections III.B and

III.C, the invalidity grounds raised in the Petition are very different than those appealed by Samsung and Formycon to the Federal Circuit. And Regeneron's appeal of the district court's denial of its PI motion against Amgen did not even involve the validity of *US865*, only non-infringement. Also, the appeals concerned only preliminary rulings; the vast majority of the pre-trial and trial proceedings are yet to come, including claim construction, as is any appeal of a trial decision. The investment into the appeals of a PI decision does not moot or obviate the need for final relief by this Board.

Thus, the parties' investment in the Federal Circuit appeals do not support discretionary denial.

3. Celltrion did not Delay in Filing this Petition

Celltrion filed its Petition on January 15, 2025, with an accorded filing date of February 14, 2025. Thus, Celltrion filed its Petition within three months of the date of service. As discussed in Section IV.C, Regeneron's original complaint asserted that Celltrion infringed 38 patents; Regeneron chose to limit its PI motion to *US865* only in its reply to Celltrion's opposition to Regeneron's motion for a PI.

Moreover, Celltrion did not wait to file petitions challenging Regeneron's patents until after it was sued by Regeneron. As explained in Section II.B, Celltrion filed multiple petitions and joinder petitions against patent claims covering aflibercept, including *IPR462*, addressing claims that contained the

stability limitations required by the challenged claims of *US865*, which Regeneron asserts render the claims patentable here. Thus, Celltrion did file petitions against many of the patents within Regeneron's 75+-patent thicket pertaining to Eylea, and did so well before Regeneron filed suit against it in the West Virginia district court or served its complaint. It simply was not practical for Celltrion—or any other litigant—to file petitions against all of the members of Regeneron's patent thicket, which indeed is the tactical goal of a thicket. Regeneron should not be rewarded for burying litigants like Celltrion in overlapping, duplicative patents with a discretionary denial here. Furthermore, as discussed in Section IV.A, Celltrion filed its Petition before scheduling of trial.

Regeneron has thus failed to demonstrate that this factor favors denial of institution.

D. Parties in Parallel Litigation

US865 was at issue in the *Mylan* trial. Although the *Mylan* trial is complete as to *US865*, Celltrion was not a party to that litigation and very different invalidity grounds were asserted. Contrary to Regeneron's assertion, there is little overlap between that trial and the district court PI proceedings involving Celltrion and Regeneron. Moreover, due to preliminary nature of the PI proceeding and the limited briefing, Celltrion only presented a single paragraph of argument as to written description in its PI opposition. This single paragraph does not overlap at

all with Mylan's arguments in the *Mylan* trial. Given the preliminary nature of the district court proceeding, and Celltrion's stipulations in Section IV.A, this factor does not counsel for discretionary denial.

E. Other Factors

As discussed below, there are other factors that the Board may consider in determining whether to exercise its discretion to deny institution. *See* Acting Director Stewart's Memorandum issued on March 26, 2025, 2-3. All of them weigh against discretionary denial.

1. Whether the PTAB or Another Forum has Already Adjudicated the Validity or Patentability of the Challenged Patent Claims

Section II.B discusses the numerous petitions and joinder petitions that Celltrion filed at the PTAB against multiple of the patents from Regeneron's patent thicket covering Eylea. Every claim that has been challenged before the PTAB has been cancelled. *Id.*

Unsurprisingly, Regeneron, in its brief, focuses solely on proceedings before the district court and Federal Circuit. But as explained in Section II.B, Celltrion was not involved in the *Mylan* trial. Regardless, once Regeneron settled with Mylan, the district court's decision was vacated before the Federal Circuit could rule on its correctness. In addition, the preliminary injunction motion was exactly that, preliminary, and the district court's order granting Regeneron's motion for PI

is not binding on the court or the parties in the full trial proceedings. As explained in Section III.A, Celltrion's opposition was limited to twenty-five pages, in which Celltrion had to address the invalidity of two patents, the economic factors of nexus and irreparable harm, and the other equitable injunction factors. Its preliminary arguments as to written description were thus necessarily very cursory, limited to a single paragraph. The district court also declined to hold a hearing on Regeneron's motion for a PI before essentially adopting Regeneron's proposed order as its decision granting Regeneron's motion for a PI. In addition, once a trial is finally scheduled, and assuming Regeneron continues to assert *US865*, Celltrion, as well as the other PI defendants, will not be limited to the invalidity defenses or evidence raised in the PI proceedings.

Thus, this factor does not favor discretionary denial, and is, at worst, neutral.

2. The Strength of the Unpatentability Challenge

The merits of the unpatentability challenges in the Petition, including the challenge to priority, are very strong. As discussed in Section III.A, the Petition does not repeat the written description arguments Celltrion made to the district court in its opposition to Regeneron's motion for PI, and thus were not previously decided by the district court. Moreover, Regeneron's assertions (Br. 40-41) that the written description issues underlying the priority challenge have already been decided by the district and appellate courts are contrary to the preliminary nature of

the proceedings, including the fact that Celltrion’s briefing on written description was limited to a single paragraph in its opposition to Regeneron’s motion for a PI. Regeneron’s assertions that Celltrion’s priority challenges are merely a rehash of what was rejected by the district court are also belied by its own expert’s testimony in *IPR462*, which was not presented to the district court, as well as Regeneron’s request for adverse judgment after institution in that proceeding. *See* Section II.A. Sections III.B and III.C discuss how the testimony of Regeneron’s expert, Dr. Klibanov, directly contradicts the district court’s finding that claim limitations in *US865* have “common structural features,” including the “very specific” VEGF antagonist⁸ and the categories of organic cosolvent buffer, and stabilizing agent, whose structures were well known in the art. That is, even if the structures were known, changing them could effect the stability of the formulation in unpredictable ways. Sections III.B and III.C. The merits of the actual anticipation and obviousness challenges are extremely strong since the primary reference is

⁸ The claims of *US865* recite a “VEGF antagonist fusion [that] **comprises** amino acids 27-457 of SEQ ID NO:4,” and the fusion protein can thus have any number of amino acids or other substituents at either or both ends of the molecule, as long as it acts as a VEGF antagonist at some level. Pet., 22-23. The claims are therefore not limited to a “very specific” VEGF antagonist.

Regeneron’s own published application, *US432*, which has the same disclosure as *US865*. See *Solus Adv. Mats. Co., Ltd. v. SK Nexilis Co., Ltd.*, IPR2024-01463, Paper 14, 12-19 (in undertaking a *Fintiv* analysis, where the parties are the same and the litigation is likely to predate the final written decision, in weighing the *Fintiv* factors, and “in particular, the strength of Petitioner’s showing,” declining to exercise discretion to deny trial).

Regeneron argues further that this is the second petition filed against *US865*, citing *Ericsson, Inc. v. Uniloc 2017, LLC*, IPR2019-01550, Paper 8, 15, for the proposition that a single petition is more than sufficient to challenge a single patent. Br., 41-42. Regeneron argues it is unfair that co-defendants have split up various invalidity theories that have already been litigated to file separate, serial, petitions. *Id.*, 42.

As an initial matter, Celltrion did not have input into Samsung’s petition, and did not review it before it was filed. *E.g.*, *Ericsson*, IPR2019-01550, Paper 8, 11 (noting that “Petitioner acknowledge[d] reviewing the prior petitions filed to determine grounds to be advanced in this proceeding.”). The challenges in the instant petition are also very different from the challenges presented by Samsung. *E.g.*, *id.*, 12 (finding that petitioner created such a relationship with the prior petitioners by using their work as a menu and picking and choosing from their

work product, tying the interests of all of the petitioners together). The facts in *Ericsson* thus do not counsel for denial here.

Regeneron also contends that the Board should not expend its limited resources to institute trial here. Br. 42. Regeneron ignores, however, that the Board has already invested substantial resources to decide IPRs concerning closely-related patents, and that all challenged claims were cancelled, whether by Regeneron disclaiming the claims or the Board finding them unpatentable in a final written decision.

The strength of Petitioner's challenges, the fact that they are supported by the testimony of Regeneron's own expert provided in an IPR challenging a patent having the same specification as *US865*, as well as that every closely-related patent claim challenged before the PTAB has resulted in cancellation of the claim, all strongly counsel against the Board exercising its discretion to deny institution.

3. Settled Expectations of the Parties

Patents are a limited monopoly, with the public expecting that they are free to use the invention once a patent has expired or its claims are invalidated. *Singer Mfg. Co. v. June Mfg. Co.*, 163 U.S. 169, 185 (1896). The settled expectation of the parties, and indeed the public, is therefore that once a patent claim expires or is invalidated, it is free to use.

US865 is one of a large family of patents, and the limitations that Regeneron relied upon for patentability at the district and appellate courts—that is, 40 mg/ml of the VEGF antagonist, glycosylation, and the stability limitations—are contained in different combinations in expired, disclaimed, or cancelled claims against which the Board has entered adverse judgment. *See* Section II.B. The settled expectation is that the public is free to use formulations having those limitations.

Regeneron argues that the parties expect that Celltrion will remain enjoined until the district court conducts a trial on its invalidity defenses. Br., 39. But that counsels against the Board exercising its discretion to deny institution. The district court has not scheduled a trial and it is pure speculation as to when it may do so. In a bid to delay that trial Regeneron is also insisting that any trial schedule be dictated by possible further PI proceedings in pending cases and in future cases that have not even been filed yet, thus delaying the date by which Celltrion’s biosimilar can enter the market. *See* EX1055, 1.

4. Compelling Economic, Public Health, or National Security Interests

Celltrion is a biosimilar manufacturer and one of many biosimilar companies that has filed an abbreviated Biologics License Application (“aBLA”) for biosimilar versions of Eylea.

It is undisputed that entry of biosimilars into the market help reduce prices, and the current administration and legislature have strongly favored bringing more

biosimilars onto the market for that purpose. Thus, on April 18, 2025, the White House issued Executive Order 14273 titled “Lowering Drug Prices by Once Again Putting Americans First.” EX1056. The Executive Order states that “pharmaceutical manufacturers charged patients in our Nation more than those in other countries for the exact same prescription drugs,” and “encourage[es] the development of generic and biosimilar alternatives to higher cost brand name prescription drugs and biologics to harness competitive forces and increase access to affordable medicines.” *Id.*, Section 1. The Fact Sheet announcing the Executive Order states that the Order “increases the availability of generics and biosimilars, which can be as much as 80% cheaper than brand alternatives.” EX1057, 2; *see also* EX1062 (May 12, 2025, Executive Order discussing importance of reducing drug prices).

Several members of Congress have also introduced bills directed to increasing the availability of biosimilars. For example, Senator Dr. Rand Paul (R-KY), on April 8, 2025, “introduced legislation to streamline the approval process for biosimilars by eliminating costly and redundant clinical study requirements. Dr. Paul’s *Expedited Access to Biosimilars Act* will increase market competition, lower drug prices, and increase access to more life-saving treatments.” EX1058, 1-2.

Similarly, Senators Amy Klobuchar (D-MN) and Chuck Grassley (R-IA), Chairman of the Senate Judiciary Committee, introduced the *Preserve Access to Affordable Generics and Biosimilars Act* and the *Stop Significant and Time-wasting Abuse Limiting Legitimate Innovation of New Generics (Stop STALLING) Act*, two bipartisan bills to reduce drug prices by promoting competition and taking on Big Pharma's abuses of deals with competitors and Food and Drug Administration (FDA) petitions. EX1059. Senator Klobuchar noted:

Prescription drug prices are too high—driven up by excessive consolidation in the pharmaceutical industry and abusive business tactics that keep more affordable medications off the market and out of reach for far too many Americans.... Our bipartisan legislation would deter anticompetitive deals and sham petitions that prevent generic drugs from entering the market and prevent Americans from accessing affordable, life-saving drugs.

Id., 1. Senator Grassley further explained:

The shady efforts of some drug companies to block competition and keep drug costs high are greedy and wrong. Across the country, consumers are suffering because of it. Our bipartisan bills will help tackle these abuses and make prescription drugs more affordable for Americans.

Id.

Finally, the effect of patent thickets covering reference products held by big pharmaceutical companies are a well-recognized impediment to biosimilar market entry. Thus, on April 3, 2025, the U.S. Senate Committee on the Judiciary issued a press release listing bills led by Senator Grassley that would lower prescription drug prices. EX1060. One of those bills is the “Affordable Prescriptions for Patients Act,” which “would prevent bad actors in the pharmaceutical industry from deliberately abusing the patent system with ‘patent thickets’ to stop potential competitors from entering the marketplace. The bill would pave the way for biosimilars to compete with branded drugs and aggressively lower drug prices for consumers in the process.” *Id.*, 1.

The White House’s Executive Order and the legislative efforts, all support a public and economic policy of encouraging biosimilar products to enter the market. Reference product sponsors should not be encouraged to amass patent thickets, like amassed by Regeneron to cover its Eylea product, to extend its monopoly. Denying institution in situations like this only encourages reference product sponsors to obtain multiple, duplicative patents to avoid PTAB scrutiny of dubious claims and discourage biosimilar entrants.

Both Regeneron and the district court recognize that the price of Eylea will come down once biosimilars come on the market. EX2004, 136 (“Regeneron has

shown that CT-P42's launch will force Regeneron to reduce the prices of its Eylea products."); 140 ("Almost across the board, biosimilars lead to permanent price erosion of the reference drug. That is because their launch causes the reference drug to compete for the first time with its own formulation."); 158 ("recent survey data shows that ophthalmologists are more comfortable prescribing biosimilars today."); 159 ("Lucentis's experience thus presents applicable evidence that ophthalmology biosimilar entry will cause price erosion of the reference product, and it also suggests that Eylea's price erosion may be particularly steep.").

US865 does not cover the active agent, aflibercept, but instead claims a formulation with allegedly increased stability. All of the limitations that Regeneron assert render the claims of *US865* patentable, however, appear in other patent claims in the family that have expired or that Regeneron has disclaimed, leading to adverse judgement. *See* Section II.A. As shown Section II.A, the claims of *US992*, which are very similar to the claims of *US865*, not only had the stability limitation of the challenged claims of *US865*, but a POSA would understand that the aflibercept of the claims is glycosylated given that the claims of *US992* also specifies that the aflibercept is made in CHO cells, which necessarily results in glycosylation. *See* Pet., 49-50; EX2005, 24-25. In addition, the use of 40 mg of aflibercept, which was the focus of the *Mylan* trial before the district

court, appears in claims of patents such as US10,400,025, US9,340,594, and US7,608,261 that are now expired. Section II.A.

Regeneron may respond that Amgen has already entered the market because its request for a PI against Amgen was denied, and that Mylan's product will enter the market at some point in the second half of 2026 as a result of a settlement with Regeneron. But as additional biosimilars continue to enter the market, the price will continue to decrease. *See* EX1061, 32 (graphs demonstrating that biosimilars not only launch at a discount, but continue to decrease their prices over time, even when there are multiple biosimilars on the market). Celltrion should not be kept out of the market by claims that are not supported by the disclosure of *US865*.

The public and economic policies of decreasing drug prices, including through introducing more biosimilars into the market, as well as the fact that the pertinent limitations of the challenged claims are recited by claims which are expired or have been disclaimed by Regeneron resulting in entry of adverse judgment, strongly counsels against the Board exercising its discretion to deny institution.

5. Efficiency and Integrity of the Patent System

The Board takes “a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Fintiv*, 6. A holistic view of all the factors discussed above dictates against the Board exercising its

discretion to deny institution. Regeneron, in arguing that the district and appellate courts have already addressed the written description argument, paints Celltrion's lack of priority argument as nothing more than what has been presented to the district court. But as discussed in Sections III.B and III.C, in asserting that discretionary denial is appropriate, Regeneron ignores that the argument Celltrion made before the district court is very different from the arguments Celltrion makes in its petition, and Regeneron also ignores its own testimony that it submitted in *462IPR* but not to the trial court, as well as additional evidence that was not before the trial court. Regeneron should not be rewarded for ignoring the differences as well as its own evidence used in arguing the validity of *US992*.

Moreover, *US865* is part of a thicket of patents that Regeneron is using to keep competitors out of the market and prop up the cost of Eylea. Section II.A. Celltrion has filed multiple petitions and joinder petitions against patents in the thicket, leading to cancellation and/or invalidation of all of the challenged claims. Section II.B. Given the public interest in allowing biosimilars to enter the market, as well as the concerns over reference product sponsors gaming the patent system by amassing patent thickets so large they cannot be effectively challenged, which Regeneron continues to do, the Board should refuse to exercise its discretion to deny institution. *See* IPR2025-00031, Paper 9, 17-18 (distinguishing the Director's decision in IPR2024-01205, Paper 19, on the basis that in that IPR extensive

infringement and invalidity contentions had been served, a Markman hearing had been held and the district court had construed the disputed terms, and trial was set to start eleven months before the Board's statutory deadline). Denying institution would further embolden companies like Regeneron to create patent thickets with overlapping claims, allowing them to disclaim claims in IPRs that have been instituted because they have an unchallengeable number of similar patent claims remaining in the thicket that can be asserted in district court.

V. CONCLUSION

For the reasons set forth above, Celltrion respectfully requests that the Board find that discretionary denial is not appropriate and institute trial.

Respectfully submitted,

Dated: May 14, 2025

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

VI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 11,116 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: May 14, 2025

/ Lora M. Green /

Lora M. Green, Lead Counsel

Reg. No. 43,541

VII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,084,865 (“US865”)
1002	Declaration of Dr. Peter Tessier in Support of IPR Petition
1003	Dr. Peter Tessier <i>curriculum vitae</i>
1004	U.S. Patent Publication No. 2007/0293432 (“US432”)
1005	International Publication No. WO 2017/129685 (“WO685”)
1006	Prosecution history of U.S. Application No. 16/739,559, now U.S. Patent No. 11,084,865
1007	Prosecution history of U.S. Application No. 16/582,486, now U.S. Patent No. 11,066,458
1008	Prosecution history of U.S. Application No. 16/159,269, now U.S. Patent No. 10,464,992
1009	Excerpts from prosecution history of U.S. Application No. 15/879,294, now U.S. Patent No. 10,400,025
1010	Excerpts from prosecution history of U.S. Application No. 15/095,606, now U.S. Patent No. 9,914,763
1011	Excerpts from prosecution history of U.S. Application No. 14/330,096, now U.S. Patent No. 9,340,594
1012	Excerpts from prosecution history of U.S. Application No. 13/914,996, now U.S. Patent No. 8,802,107
1013	Excerpts from prosecution history of U.S. Application No. 13/329,770, now U.S. Patent No. 8,481,046
1014	Prosecution history of U.S. Application No. 12/833,417, now U.S. Patent No. 8,092,803
1015	Excerpts from prosecution history of U.S. Application No. 12/560,885, now US 7,807,164
1016	Excerpts from prosecution history of U.S. Application No. 11/818,463, now U.S. Patent No. 7,608,261
1017	Christine Wulff et al., <i>Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2</i> , 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) (“Wulff”)
1018	International Publication No. WO 2018/094316 (“WO316”)

Exhibit No.	Description
1019	EYLEA® Prescribing Information, November 2011 (“PI2011”)
1020	James D. Andya et al., <i>Mechanisms of Aggregate Formation and Carbohydrate Excipient Stabilization of Lyophilized Humanized Monoclonal Antibody Formulations</i> , 5(2) AAPS PHARMSCI (Apr. 4, 2003) (“Andya 2003”)
1021	Declaration of Alexander M. Klibanov submitted in support of Regeneron’s Patent Owner Response in IPR2023-00462 (Nov. 2, 2023)
1022	U.S. Patent Publication No. 2004/0197324 to Liu et al. (“Liu”)
1023	Leopold K. Kostanski et al., <i>Size-exclusion Chromatography – a Review of Calibration Methodologies</i> , 58 J. BIOCHEM. BIOPHYS. METHODS 159-186 (2004) (“Kostanski 2004”)
1024	Memorandum Opinion and Order Following Bench Trial (Dec. 27, 2023) in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.</i> , 1:22-CV-61 (N.D. WV)
1025	U.S. Provisional Application No. 60/814,484
1026	Regeneron’s Patent Owner Response in IPR2023-00462
1027	Declaration of Alexander M. Klibanov submitted in support of Regeneron’s Preliminary Response in IPR2023-00462 (Apr. 25, 2023)
1028	Jocelyn Holash et al., <i>VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects</i> , 99 (17) PNAS 11393-11398 (Aug. 20, 2002) (“Holash”)
1029	International Publication No. WO 00/75319 (“WO319”)
1030	Napoleone Ferrara & Robert S. Kerbel, <i>Angiogenesis as a Therapeutic Target</i> , 438 NATURE 967-74 (Dec. 15, 2005) (“Ferrara”)
1031	Liming Liu, <i>Antibody Glycosylation and its Impact on the Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies and FC-fusion Proteins</i> , 104(6) J. PHARM SCI 1866-1884 (Apr. 14, 2015) (“Liu 2015”)
1032	Royston Jefferis, <i>Glycosylation of Recombinant Antibody Therapeutics</i> , 21 Biotechnol. Prog. 11-16 (2005) (“Jefferis”)
1033	S. Krapp et al., <i>Structural Analysis of Human IgG-Fc Glycoforms Reveals a Correlation Between Glycosylation and Structural Integrity</i> , 325(5) J. MOL. BIOL. 979-89 (Jan. 31, 2003) (“Krapp”)

Exhibit No.	Description
1034	Y. Mimura et al., <i>Role of Oligosaccharide Residues of IgG1-Fc in gamma RIIB Binding</i> , 276(49) J. BIOL. CHEM. 45539-47 (Sep. 20, 2001) (“Mimura 2001”)
1035	-- Intentional Left Blank --
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1037	David J. Panka, <i>Glycosylation is Influential in Murine IgG3 Self-Association</i> , 34 (8-9) MOLECULAR IMMUNOLOGY 593-98 (June 1997) (“Panka”)
1038	Byeong S. Chang & Susan Hershenson, <i>Practical Approaches to Protein Formulation Development in RATIONALE DESIGN OF STABLE PROTEIN FORMULATIONS – THEORY AND PRACTICE</i> , 1-25 (J.F. Carpenter and M.C. Manning eds., 2002) (“Chang”)
1039	Dave A. Parkins & Ulla T. Lashmar, <i>The Formulation of Biopharmaceutical Products</i> , 3(4) PHARM. SCI. & TECH. TODAY 129-137 (Apr. 4, 2000) (“Parkins”)
1040	Y. Mimura et al., <i>The influence of glycosylation on the thermal stability and effector function expression of human IgG1-Fc: properties of a series of truncated glycoforms</i> , 37 (2000) MOLECULAR IMMUNOLOGY 697-706 (Sept. 2000) (“Mimura 2000”)
1041	Hanns-Christian Mahler et al., <i>Induction and Analysis of Aggregates in a Liquid IgG1-antibody Formulation</i> , 59(2005) EURO. J. PHARMA. BIOPHARM 407-17 (Jan. 19, 2005) (“Mahler 2005”)
1042	Ib Anderson, <i>Determination of Specific Proteins by FIA Principle</i> , 12(2) J. AUTO. CHEM. 53-59 (Apr. 1990) (“Anderson 1990”)
1043	U.S. Patent Publication No. 2006/0058234 (“Daly”)
1044	U.S. Patent Publication No. 2005/0175610 (“Wiegand”)
1045	Ryosuke Yumioka et al., <i>Mobile Phase Containing Arginine Provides More Reliable SEC Condition for Aggregation Analysis</i> , 99(2) J. PHARM SCI 618-620 (June 30, 2009) (“Yumioka”)
1046	Daisuke Ejima et al., <i>Arginine as an effective additive in gel permeation chromatography</i> , J. CHROMATOGR. A 1094 49-55 (Oct. 5, 2005) (“Ejima”)
1047	Aditya V. Gandhi et al., <i>Some Lessons Learned From a Comparison Between Sedimentation Velocity Analytical Ultracentrifugation and</i>

Exhibit No.	Description
	<i>Size Exclusion Chromatography to Characterize and Quantify Protein Aggregates</i> , 106 J. PHARM SCI 2178-2186 (2017) (“ <i>Gandhi</i> ”)
1048	Nonconfidential Brief of Appellee Regeneron Pharmaceuticals, Inc. in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc. et al.</i> , Doc. 36, Case Nos. 24-1965, 24-1966, 24-2082, 24-2083 (Fed. Cir., Aug. 26, 2024)
1049	Testimony of Kenneth S. Graham in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.</i> , 1:22-CV-61 (N.D. WV)
1050	Summons in a Civil Action, <i>Regeneron Pharmaceuticals, Inc. v. Celltrion</i> , No. 1:23-CV-89 (N.D.W.Va. 2023)
1051	Petitioner’s Reply to Patent Owner’s Preliminary Response, <i>Samsung Bioepis Co., Ltd., v. Regeneron Pharmaceuticals, Inc.</i> , IPR2025-00176 (Apr. 23, 2025)
1052	Reply to Patent Owner’s Preliminary Response, <i>Formycon AG, v. Regeneron Pharmaceuticals, Inc.</i> , IPR2025-00233 (Apr. 23, 2025)
1053	Decision, Adverse Judgment After Institution of Trial, <i>Celltrion Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2023-00462 (Feb. 21, 2024)
1054	Stipulation and Order Vacating Permanent Preliminary Injunction, <i>In re: Aflibercept Patent Litigation</i> , No. 1:24-MD-3103-TSK (N.D.W.Va. 2025)
1055	Exhibit 1122 (Email from Williams & Connolly LLP Regarding Alvotech), <i>Formycon AG, v. Regeneron Pharmaceuticals, Inc.</i> , IPR2025-00233 (Apr. 18, 2025)
1056	<i>Executive Order 14273, Lowering Drug Prices by Once Again Putting Americans First</i> , Federal Register (Apr. 15, 2025), https://www.federalregister.gov/documents/2025/04/18/2025-06837/lowering-drug-prices-by-once-again-putting-americans-first
1057	<i>Fact Sheet: President Donald J. Trump Announces Actions to Lower Prescription Drug Prices</i> , The White House (Apr. 15, 2025), https://www.whitehouse.gov/fact-sheets/2025/04/fact-sheet-president-donald-j-trump-announces-actions-to-lower-prescription-drug-prices/
1058	<i>Dr. Rand Paul Introduces Legislation to Cut Bureaucratic Red Tape and Lower Drug Prices</i> , Dr Rand Paul US Senator Kentucky (Apr. 8, 2025), https://www.paul.senate.gov/dr-rand-paul-introduces-legislation-to-modernize-fda-prescription-drug-approvals-and-lower-drug-prices/#:~:text=Paul%E2%80%99s%20Expedited%20Access%20to%20Biosimilars%20Act%20will%20increase,prices%2C%20

Exhibit No.	Description
	and%20increase%20access%20to%20more%20life-saving%20treatments
1059	<i>Klobuchar, Grassley Introduce Bipartisan Bills to Reduce Drug Prices by Promoting Competition and Taking on Big Pharma</i> , United States Senator Amy Klobuchar (Mar. 26, 2025), https://www.klobuchar.senate.gov/public/index.cfm/2025/3/klobuchar-grassley-introduce-bipartisan-bills-to-reduce-drug-prices-by-promoting-competition-and-taking-on-big-pharma
1060	<i>Senate Judiciary Committee Advances Grassley-Led Bills to Lower Prescription Drug Prices</i> , U.S. Senate Committee on the Judiciary (Apr. 3, 2025), https://www.judiciary.senate.gov/press/rep/releases/senate-judiciary-committee-advances-grassley-led-bills-to-lower-prescription-drug-prices
1061	<i>The U.S. Generic & Biosimilar Medicines Savings Report</i> , Association for Accessible Medicines (Sept. 2024).
1062	<i>Delivering Most-Favored-Nation Prescription Drug Pricing to American Patients</i> , The White House (May 12, 2025), https://www.whitehouse.gov/presidential-actions/2025/05/delivering-most-favored-nation-prescription-drug-pricing-to-american-patients
1063	Nonconfidential Opening Brief for Defendant-Appellant Samsung Bioepis Co., Ltd., <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals</i> , No. 24-1965 (Fed. Cir. July 17, 2024)

CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. § 42.6(e), I hereby certify that on May 14, 2025, true and correct copies of Petitioner's Opposition to Patent Owner's Discretionary Denial Brief (and accompanying Exhibits 1050-1063) were filed on P-TACTS today and served via electronic mail to Patent Owner at the following email addresses of record:

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