

No. 24-2058, 24-2147

In the
United States Court of Appeals
For the Federal Circuit

REGENERON PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MYLAN PHARMACEUTICALS INC., AMGEN USA, INC., BIOCON
BIOLOGICS INC., SAMSUNG BIOEPIS CO., LTD., FORMYCON AG,
AMGEN INC.,

Defendants,

CELLTRION, INC.,

Defendant-Appellant.

Appeal from the U.S. District Court for the Northern District of West
Virginia in No. 1:24-md-3103-TSK, Judge Thomas S. Kleeh

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INTRODUCTION

Regeneron does not dispute that the district court’s wholesale adoption of its proposed order warrants careful scrutiny from this Court. And although laden with platitudes, Regeneron’s brief offers little evidence, case law, or public policy from which the district court’s deeply flawed order might survive such review.

From the outset, Regeneron distances itself from its own proposed reasoning, declining to defend the district court’s view that the ’594 patent’s terminal disclaimer did not curtail its 20-year statutory term, but merely rendered some portion “unenforceable.” Instead, Regeneron now argues that the ’594 patent is not a proper ODP reference because, as long as a patentee does not obtain a patent term adjustment, no patent can serve as an ODP reference to other patents within the same family sharing the same priority date. That new argument is contrary to this Court’s cases and no public policy commends it. To the contrary, it would vitiate the safeguards to the public’s interest provided by ODP, render terminal disclaimers substantially meaningless, deprive the public of certainty about when it is free to practice an expired claim, and invite

additional gamesmanship in the erection of thickets of overlapping patents that already plague the pharmaceutical industry.

Regeneron's additional arguments are no more persuasive. Regeneron repeatedly complains that Celltrion improperly uses the common specification of the '594 and '865 patents as prior art in analyzing whether purported differences between reference claim 5 and the asserted claims are patentable. Regeneron's desire to avoid this Court's close scrutiny of the specification is understandable, since the specification reveals there are no patentable differences. It informs a POSA that reference claim 5 is narrowly drawn to Regeneron's commercial EYLEA formulation of aflibercept—a prior-art glycoprotein—and explains in clear detail that the allegedly patentable differences between claim 5's formulation and the asserted claims regarding glycosylation and stability are all known features of this commercial EYLEA formulation. Far from prohibiting the Court from considering such relevant evidence, the law requires it.

Regeneron also confusingly accuses Celltrion of blending the concepts of anticipation and obviousness into a new doctrine. Nonsense. In its opening brief, Celltrion meticulously explained, on a limitation-by-

limitation basis, how reference claim 5 *either* anticipates *or* renders obvious the five alleged patentable distinctions cited by the district court. Each of those alternative arguments is separately and clearly labeled for the Court to consider. Regeneron provides no sound reason—in law or logic—for requiring Celltrion to group its invalidity arguments by doctrine instead of limitation.

Finally, it is Regeneron that has fashioned new doctrine, defending the district court’s confusion about the law governing “teaching away” by creating a new test for prior art that “motivates against” without teaching away. That is empty semantics. Semantics aside, while the court found—erroneously—that the prior art suggested that non-glycosylated proteins, mini-VEGF traps, and pre-filled syringes might have advantages over the aflibercept and vial packaging of the asserted claims, the law is clear that the prior art must do more than teach that there are better or preferred options to aflibercept and vials, both of which were known, workable options for intravitreal formulations. Regeneron cannot reasonably assert that the prior art—when correctly examined as a whole—taught or suggested that EYLEA containing aflibercept and placed in a vial would have no utility in the claim 5

intravitreal composition. And beyond the prior art, the specification indisputably establishes this utility.

For these reasons, and those elaborated further in Celltrion's opening brief and herein, Celltrion respectfully requests that the Court reverse the district court's preliminary injunction order.

ARGUMENT

I. Regeneron Has Failed To Demonstrate A Likelihood Of Success On The Validity Of The '865 Patent

A. The '594 Patent is a Proper ODP Reference Patent Against the '865 Patent

The earlier-filed, earlier-expiring, and commonly-owned '594 patent is a proper ODP reference patent to its progeny '865 patent. Regeneron does not dispute that the statutory term of the '594 patent ended more than six years before the expiration of the '865 patent, nor does it defend the district court's erroneous conclusion that Regeneron's terminal disclaimer merely rendered some portion of the '594 patent's statutory term "unenforceable" without curtailing that term. Instead, Regeneron's principal rebuttal argument is that "the '594 patent is not a proper double-patenting reference patent, because forgoing term in the

'594 patent in no way extends the 20-year term of the '865 patent.” Resp. Br. (“RB”) 19.

That argument plainly fails. The ODP issue here is not whether the 20-year term of the '865 patent has somehow been extended, but whether the later-filed, later-issued, and later-expiring '865 patent extended Regeneron's patent term for the invention of claim 5 of the first-filed, first-issued, and already-expired '594 patent. Assuming that the asserted claims of the '865 patent cover the same EYLEA formulation as reference claim 5 of the '594 patent, or obvious variants thereof, Regeneron cannot credibly dispute this extension. Regeneron's rebuttal thus misses the point.

What Regeneron really appears to be arguing is that it remained entitled to a 20-year term for the invention of reference claim 5 even after it made the voluntary choice to curtail the term of that invention with a terminal disclaimer. In Regeneron's view, ODP cannot bar Regeneron from undoing the disclaimer with a second-filed, later-issuing patent to the invention of claim 5 as long as that second patent does not receive PTA extending the term beyond 20 years. This sweeping assertion is

contrary to this Court's precedent, the law governing terminal disclaimers, and the public policy foundational to ODP.

Terminal disclaimers, like PTAs, modify the 20-year statutory term of patents. Opening Br. ("Br.") 28-31. These disclaimers may not be undone once the patent issues, in part because they serve a crucial public notification function about when the public is free to use the claimed subject matter. *Id.* 33-34. Here, the public was entitled to rely on Regeneron's terminal disclaimer to know when it was free to practice the invention of reference claim 5 and its obvious variants. Under Regeneron's view, that certainty would be cast aside. The public would either have to forego practicing an expired patent for the duration of the disclaimed term, or risk the possibility of infringing a hypothetical later-filed, second patent that may never materialize.

This is antithetical to the fundamental policies behind the patent grant discussed in *Gilead Sciences Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014). There, the Court noted that it is a "bedrock principle of our patent system" that the public may freely use an expired patent's inventions and obvious modifications thereof, which is "violated" when the inventor nevertheless retains his monopoly through "another

later-expiring patent with claims for obvious modifications of the invention.” *Id.* at 1214; *see also In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982) (quoting *In re Schneller*, 397 F.2d 350 (C.C.P.A. 1968) (“The fundamental reason for the rule [of ODP] is to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about.”)).

The Court has confirmed that ODP is necessary to protect those fundamental policies even where the earlier- and later-expiring patents lie within the same family and share a common priority filing date. In *AbbVie v. Mathilda & Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366 (Fed. Cir. 2014), the Court observed that the problem of obtaining a second, later-expiring patent still exists within a patent family sharing the same priority filing date, and ODP is a necessary safeguard to ensure that a particular invention (or obvious variants thereof) does not receive an unjustified patent term extension. *Id.* at 1373; *see also Allergan USA, Inc. v. MSN Lab’ys Private Ltd.*, 111 F.4th 1358, 1367 (Fed. Cir. 2024) (“[A] common priority date does not always guarantee a common expiration date.”); *In re Lonardo*, 119 F.3d 960, 965-67 (Fed. Cir. 1997) (instituting reexamination on the basis of ODP over

patents sharing the same priority date was proper); *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1354 (Fed. Cir. 2009) (remanding for analysis whether claims granted from continuation applications were invalid for ODP).

There is also nothing unfair in holding Regeneron to the bargain it struck with the public when it filed the terminal disclaimer. Regeneron chose to erect a multi-family, interwoven thicket of continuations covering the EYLEA formulation. As part of that prosecution strategy, it chose to file a terminal disclaimer to overcome the examiner's ODP rejection of the '594 patent's claims over the '261 patent rather than contest that rejection on the merits. It did so knowing that the '261 patent's term was curtailed by yet another voluntary disclaimer over the '173 and '757 patents, one of which had an earlier priority filing date.

While Regeneron insists that it obtained no advantage from this state of affairs, it certainly obtained the advantage of an expedient disposal of the examiner's ODP rejection and thus early patent protection for EYLEA. Even if it had not, that is of no moment. The time to argue that the '261 patent's terminal disclaimer should not curtail the term of the '594 patent was during prosecution, before Regeneron made the

decision to link the expiration of the '594 patent to that of the '261 patent. There is nothing unfair about holding Regeneron to the consequences of its prosecution strategy.

None of the other cases Regeneron cites supports its argument. *Ezra* concerned the interplay between ODP and a patent term extension (PTE) granted under 35 U.S.C. § 156. *Novartis AG v. Extra Ventures LLC*, 909 F.3d 1367, 1373-74 (Fed. Cir. 2018). There, the Court interpreted § 156 as providing a statutory exemption shielding PTEs from ODP. But PTEs are not at issue here, and no such exemption applies to terminal disclaimers. As Celltrion explained in its opening brief, to the extent *Ezra* speaks to the issues before this Court at all, it undermines the district court's flawed reasoning that § 154(a)'s 20-year term cannot be altered for purposes of ODP by other provisions of the patent statute, such as those governing PTAs, PTEs, and terminal disclaimers. *See* Br. 30.

Far from supporting Regeneron, *Allergan* squarely confirms the application of ODP. There, the Court emphasized that the purpose of ODP is "to prevent patentees from obtaining a *second* patent on a patentably indistinct invention to effectively extend the life of a *first*

patent to that subject matter.” *Allergan*, 111 F.4th at 1369. This case presents the same fact pattern: The ’594 patent is the first-filed, first-issued patent to the EYLEA formulation, and it sets the patent term for that invention. The ’865 patent is the second-filed, later-issued, and later-expiring patent that would, if not for the operation of ODP, effectively extend Regeneron’s original patent term for the subject matter of claim 5.

Finally, in *Merck Sharp & Dohme v. Teva Pharmaceuticals USA*, 217 F. Supp. 3d 782 (D. Del. 2016), the court examined whether a later-filed, later-issued, but earlier-expiring continuation could serve as an ODP reference patent to its parent. *Id.* at 787. The *Merck* court held it could not. But that says nothing about whether the earlier-filed, earlier-issued, and earlier-expiring *parent* ’594 patent should be deemed a valid ODP reference against its later-filed, later-issued, and later-expired *child* continuation ’865 patent. And as this Court held in *Allergan*, ODP applies.

In sum, Regeneron cites no authority to support the district court’s erroneous conclusion that the ’594 patent is not a proper ODP reference patent.

B. Celltrion Established a Substantial Likelihood that the '865 Patent is Invalid Over the '594 Patent

Regeneron recounts only three limitations that it contends render the asserted claims patentably distinct from reference claim 5: (1) placing the formulation in a vial; (2) requiring the glycan structure of aflibercept; and (3) requiring at least 98% of the aflibercept be present in native conformation after storage. None renders the asserted claims patentably distinct from reference claim 5.

Although Regeneron feigns confusion as to the doctrinal reasons for that conclusion, Celltrion's opening brief clearly articulated its view. First, reference claim 5's teaching of EYLEA in a pre-filled syringe combined with a POSA's knowledge that a vial is an acceptable and simpler packaging medium render obvious the vial limitation of claims 4, 7, 9, 11, and 14-17. Second, in light of the intrinsic evidence, claim 5 is properly construed as claiming the use of aflibercept with its glycans intact. But if construed as claiming a genus of glycosylated and non-glycosylated variants, that genus either anticipates or renders obvious the glycosylation limitation of the asserted claims. Third, claim 5's four-month stability requirement is properly construed as anticipating the asserted claims' two-month, 98% native-conformation requirement. If, as

Regeneron wrongly advocates, the asserted claims are construed to require highly-purified aflibercept prior to storage, this would have been obvious to a POSA.

As these are the only purported distinctions on which Regeneron relies, claims 4, 7, 11, and 14-17 are each rendered obvious by claim 5, and the remaining asserted claims are either anticipated, or alternatively rendered obvious, by reference claim 5.

1. Placing the Formulation in a Vial Does Not Make the Asserted Claims Patentably Distinct From Reference Claim 5

At the outset, the Court can quickly dispatch Regeneron's feeble rationalization of the district court's indefensible holding that placing EYLEA in a vial justifies six years of additional patent term. Regeneron does not contest that vials were a well-known packaging option for injectable biologic formulations like EYLEA that would have yielded the trivial, predictable success of being an adequate vessel to contain that product. Br. 38. Despite Regeneron's claim to the contrary (RB 59-60), that is all that is required for an obviousness showing. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). The act of placing EYLEA in an acceptable, conventional package like a vial does not suddenly become

patentable simply because an improved packaging option like a PFS comes along. That is especially true where, as here, using the old, conventional packaging to contain EYLEA is not alleged to produce some unexpected benefit.

Even if Regeneron were correct that the law demands proof that a POSA would perceive vials to have some advantage over PFSs, Regeneron does not contest that its own expert, Dr. Trout, acknowledged that the development of a vial presentation is less complicated than the development of a PFS presentation. Br. 38. The record thus shows an uncontested “motivation to modify” reference claim 5 to use a vial rather than a PFS. The district court’s erroneous opinion makes no mention of this countervailing evidence.

2. Glycosylation Does Not Render the Invention of the Asserted Claims Patentably Distinct from the Invention of Claim 5 of the ’594 Patent

A POSA would have readily understood from the specification and common knowledge in the field, as evidenced by *Daly*, that the VEGF trap of reference claim 5 is aflibercept—a glycoprotein—or, in the alternative, would have been able to envision that aflibercept was a species within the alleged genus of reference claim 5. For these reasons,

the VEGF trap of reference claim 5 anticipates the VEGF trap of the asserted claims. But even if the Court finds no anticipation, it would have been obvious for a POSA to use aflibercept—with its glycans intact—in the formulation of claim 5 in light of the prior art and the teachings within the claim itself. *See* Br. 47-56. Regeneron’s arguments to the contrary are unpersuasive.

a. A POSA Would Understand the VEGF Trap of Reference Claim 5 to Be the Glycoprotein Aflibercept

Regeneron argues that absent a “clear and unmistakable” disclaimer in the specification, reference claim 5 must be construed as encompassing both aflibercept, a known glycoprotein, and an unknown, undescribed, hypothetical variant of aflibercept that has been stripped of its glycans. But the intrinsic evidence makes clear and unmistakable to a POSA that “the VEGF trap” of reference claim 5 “consist[ing] of amino acids 27-457 of SEQ ID NO:4” is aflibercept, with its glycans intact. Regeneron does not dispute that the specification mentions a VEGF trap consisting of amino acids 27-457 of SEQ ID NO:4 only once: “[i]n a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308.”

Appx08285, 6:4-7. Nor does Regeneron contest that the only method of making a VEGF trap disclosed in the specification is to express the trap in CHO cells, which were known to post-translationally attach N-linked glycans at particular amino acid consensus sequences within a protein's primary amino acid structure. Appx08285, 6:2-4; Appx10683-10687 ¶¶162-70. Nor does Regeneron dispute that a POSA would have discerned from SEQ ID NO:4, disclosed in the specification, that amino acids 27-457 of that sequence contain five such N-linked glycosylation sites at Asn residues 62, 94, 149, 222, and 308. Appx10687 ¶170 (citing Appx12761-12769, 154:1-162:4; Appx12781-12782, 174:11-175:7).

Even more telling, both Regeneron and its expert acknowledged that a POSA would have understood the VEGF trap used in the examples, which is described only as "SEQ ID NO:4" without expressly mentioning its glycan structure, to be aflibercept with its glycans intact. Appx10687 ¶170.

Tellingly, the specification makes no mention of Regeneron's unknown, undescribed, hypothetical variant of aflibercept that has been stripped of its glycans. Reference claim 5 requires that the formulation be "stable for at least 4 months." The parties agree that glycans can affect

the stability of fusion proteins. Appx10709-10 ¶¶241-42 (citing Appx12411). The only mention of stability in the specification is in the examples, which use intact aflibercept. While Regeneron complains that “the claims are not limited to the examples,” if reference claim 5 indeed covers Regeneron’s imaginary, non-glycosylated fusion protein, it would lack written description support under 35 U.S.C. § 112. That purported invention is simply not disclosed.

Regeneron responds that there cannot be a clear disclaimer because “the experts agreed that ‘aflibercept can be produced from different cells, only some of which result in glycosylation.’” RB 35. But the passage cited by Regeneron does not mention aflibercept at all, and the specification does not mention the “mutant CHO cells” that were the subject of the questioning. *See* Appx00088, Appx00409-Appx00414. Again, the fact that the specification does not describe any variant of aflibercept with its glycans removed, or any method of making such a variant, weighs heavily against Regeneron’s overbroad construction.

Regeneron also responds that reading glycosylation into claim 5 of the ’594 patent would render the express recitation of glycosylation in the asserted claims meaningless. RB 32. But the specification is the single

best guide in construing the meaning of a disputed term. Where, as here, the specification makes clear that the VEGF trap of claim 5 is intact aflibercept, claim term redundancy should not inflexibly dictate claim construction. *Vitrionics Corp. v. Conception, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see also Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1371 (Fed. Cir. 2017) (“Although [this Court] ha[s] in some instances interpreted claim terms to avoid redundancy, the rule is not inflexible.”). That is especially true given the origins of the redundancy here. The asserted claims merely tack on descriptions of the glycosylation and stability of the reference claim 5 formulation that a POSA undisputedly would have gleaned from Examples 3 and 4. Those descriptions are, in fact, redundant, tacked on in a bid to obtain a second patent to the commercial EYLEA formulation of claim 5 having an extended patent term.

b. In the Alternative, A POSA Would Understand the VEGF Trap of Reference Claim 5 to at Least Include the Glycoprotein Aflibercept

Even if this Court concludes that the VEGF trap of reference claim 5 is not *limited* to aflibercept with its glycans intact, but instead constitutes a genus of glycosylated and non-glycosylated “species,” a

POSA would have understood from the intrinsic evidence that claim 5 *includes* intact aflibercept.

Regeneron glosses over the district court’s conclusion that a POSA would have understood reference claim 5 to cover both glycosylated and non-glycosylated “species” of aflibercept—a genus of two. RB 36. In those circumstances, the ordinary artisan would immediately envision that the genus would include glycosylated species. *In re Petering*, 301 F.2d 676, 683 (C.C.P.A. 1962). This settles the issue for the majority of the asserted claims, which require only that the VEGF trap be glycosylated, without regard to any specific glycan structure.

As for claims 14 and 39—which require glycosylation at the five specific asparagine residues glycosylated in aflibercept—Regeneron contends that the district court correctly found that there are at least thirty different possible glycosylated aflibercept species, a number the court found was a “not very small” genus. RB 36, 38. But if, as Regeneron asserts, a POSA would envision claim 5 as covering a hypothetical species of aflibercept, undescribed in the specification or prior art, that contains no glycans at any of the five sites within the claimed amino acid sequence, then surely it is no great stretch to conclude that the POSA would also

envision claim 5 as covering a species with all five sites occupied. Regeneron's math is not persuasive.

And while Regeneron strenuously objects to a POSA consulting the specification to determine which species the inventors intended the supposed genus to cover, it offers no reason why that consultation to gauge claim scope offends any principles of claim construction. Since the POSA would be examining just those portions of the specification that concerned the claimed genus, the POSA would not be using the specification "as prior art." *See In re Vogel*, 422 F.2d 438, 442 (C.C.P.A. 1970) (The "use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. § 103, since only the disclosure of the invention claimed in the patent may be examined."). Indeed, the Court has used the specification in precisely this manner. *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1378-79 (Fed. Cir. 2008) (using specification of earlier patent to gauge which olefins "were intended to fall within the meaning of the [earlier-issued] claims.").

Regeneron also argues that it would be improper to rely on *Daly*, since anticipation requires that all claim limitations be described in a

single reference. RB 40. But Celltrion merely points to *Daly* as evidence of the state of the art that would have been understood by a POSA, *i.e.*, that the only known VEGF trap consisting of “amino acids 27-457 of SEQ ID NO:4” was aflibercept, and that aflibercept is glycosylated at asparagine residues 62, 94, 149, 222, and 308. Br. 49. And the Court has been crystal clear that “species are unpatentable when *prior art disclosures* describe the genus containing those species such that a [POSA] would be able to envision every member of the class.” *AbbVie*, 764 F.3d at 1379 (emphasis added). This is so whether that envisioning falls under the label of claim construction, anticipation, or obviousness.

c. At a Minimum, the VEGF Trap of Reference Claim 5 Renders Obvious the Glycosylated VEGF Trap of the Asserted Claims

In any event, the prior art provides extensive motivation for a POSA to use intact, glycosylated aflibercept and not some hypothetical, untested variant stripped of its glycans. As explained in Celltrion’s opening brief, the district court committed reversible error in finding that a POSA would have been “motivated against” using glycosylated aflibercept because it would increase: (1) the size of aflibercept, reducing retinal penetration; (2) systemic exposure; and (3) the risk of

inflammation. Br. 47-56. Regeneron’s efforts to defend those findings—based principally on the very different record in the *Mylan* case—fall short.

Two points warrant addressing at the outset. First, the record in *Mylan* is irrelevant to this case. As Regeneron acknowledges (RB 10), *Mylan* relied principally on prior art involving ranibizumab. Here, the closest prior art is claim 5 of the ’594 patent, which, like the asserted claims, is drawn to the EYLEA formulation. Celltrion also raised additional prior art not of record in *Mylan*, including Regeneron’s publication of the fact that it had successfully administered aflibercept¹ intravitreally in humans. The opinions of Celltrion’s expert, Dr. Tessier, were also very different than those of *Mylan*’s experts, since ODP over reference claim 5 was not at issue in *Mylan*. It was error for the district court to rely so heavily on the factual findings from the *Mylan* litigation.

¹ Regeneron’s publications refer to aflibercept by an earlier name, “VEGF Trap-Eye.” See, e.g., Appx11974-Appx11978; Appx12001-Appx00004. Dr. Tessier explained that a POSA would have understood that the VEGF Trap-Eye molecule was the same molecule having the glycan structure and amino acid sequence published in *Daly*. See Appx10653-54 ¶81, Appx10707 ¶235, Appx10715 ¶¶252-53.

Second, Regeneron improperly attempts to distinguish between prior art that “taught away” from using aflibercept and prior art that merely “motivated against” such use. RB 41. This Court’s rigorous standard for “teaching away” cannot be so readily circumvented. Prior art does not teach away or “motivate against” simply because it suggests there may be advantages to VEGF traps other than a known, workable option like aflibercept. Rather, the art must actually discourage a POSA from using aflibercept, *e.g.*, by teaching or suggesting that it would not have utility in the formulation of claim 5. *Bayer Pharma AG v. Watson Lab’ys, Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017).

Here, as explained, aflibercept was a known—indeed the only known—VEGF trap having the sequence required by claim 5. The prior art contained many disclosures extolling the safety of this known option, including its superior safety, pharmacokinetics, and efficacy over other VEGF traps that had been successfully administered intravitreally, including bevacizumab and ranibizumab. Br. 8. Crucially, as explained, Regeneron published successful clinical testing of intravitreal aflibercept in humans.

Nonetheless, largely ignoring the prior art concerning aflibercept, the district court repeatedly found that prior art which *did not concern aflibercept*, and—under the most charitable interpretation—merely suggested that smaller VEGF traps may have advantages over aflibercept (or other antibody-like intravitreal VEGF traps like bevacizumab), constituted a “motivation against” aflibercept and was fatal to obviousness. The court never held that this art taught or suggested aflibercept would have no utility in the claim 5 formulation; nor could it since the portions of the art cited by the court did not even concern aflibercept. Indeed, the court’s discussion of prior art in this regard is a side-show since the specification itself shows that aflibercept has utility in the reference claim 5 formulation. *See AbbVie, Inc.*, 764 F.3d at 1380 (finding ODP where the later-expiring patent merely claimed the utility of the earlier-expiring patent’s claimed subject matter that was disclosed in its specification). This was legal error.

i. Retinal Penetration

As for the particular grounds for teaching away, Regeneron first asserts that Celltrion failed to demonstrate clear error in the district court’s finding that the prior art demonstrated that a molecule greater

than 77 kDa in size would not freely penetrate the “retinal barrier.” RB 43. But that finding is based on prior art drawn to ranibizumab, not aflibercept, and on *Ghate* and *Jackson*, which also did not concern aflibercept. RB 43-44 (citing *Gaudreault*, Appx00093 (quoting Appx07246, Appx07251)). Reference claim 5 actually teaches that a molecule at least as large as 97 kDa, far larger than ranibizumab and the “retinal barrier,” is “suitable for intravitreal administration.” See Br. 51-54. And as explained in Celltrion’s opening brief, prior art that post-dates *Ghate* and *Jackson* reported clinical success with both intravitreal aflibercept and bevacizumab, which is larger than aflibercept and is glycosylated. Br. 53-54.

Regeneron improperly asserts that *Daly* teaches only the use of mini-traps smaller than aflibercept. RB 47. But even according to Regeneron, *Daly* merely suggested that Regeneron’s “mini-traps” had “optimized characteristics for local, intravitreal delivery.” RB 44. This does not teach that aflibercept would not be useful in the intravitreal formulation of claim 5.

ii. Systemic Half-Life

Regeneron next contends that the undisputed evidence of record established that “glycosylation lengthened the half-life of proteins in serum,” whereas *Daly* taught that shorter serum half-life was desirable for VEGF traps. RB 48. But again, aflibercept was a known option for inclusion in claim 5, and indeed the only known option that met the claim’s requirements. *Daly* does not suggest that a shorter half-life than aflibercept possessed is what was required for an intravitreal VEGF trap or that aflibercept would not be useful in the reference claim 5 formulation. Further, the court ignored Dr. Tessier’s testimony that a POSA would have viewed increased systemic exposure caused by a longer half-life as a non-issue, or even a benefit. Appx10721-Appx10722 ¶ 267-70. The court was not free to cherry-pick the evidence, but should have impartially and fully considered Dr. Tessier’s testimony about the prior art as a whole.

iii. Potential Immune Response

Regeneron finally asserts that Celltrion has not shown clear error in the district court’s finding that *Daly* taught that glycosylation was understood to activate immune-mediated toxicities in molecules

possessing an Fc region, like aflibercept. RB 49. *Daly* characterized aflibercept, with its glycans intact, as a useful VEGF trap and did not teach that it was toxic. The court’s inference is completely unsupported. The court also ignored that bevacizumab, a glycosylated antibody with an Fc region, and aflibercept had been successfully administered to humans. Br. 55-56.

3. The Stability Limitations of the Asserted Claims Do Not Render Them Patentably Distinct from Reference Claim 5

When properly construed, the asserted claims require only that at least 98% of the VEGF trap present before storage at 5° C for two months be present in “native conformation” (as measured by SEC) after that storage. When the limitation of “stable for at least 4 months” of reference claim 5 is properly construed, it is clear that the formulation of claim 5—Regeneron’s commercial EYLEA formulation—meets the stability limitation of the asserted claims. And even if the Court adopts Regeneron’s proposed construction of the asserted claims, which seeks to wrongly impose a requirement that the VEGF trap used to make the formulation be at least 98% pure *prior* to storage, that initial purity would have been obvious.

a. Properly Construed, Reference Claim 5's "Stable For at Least 4 Months" Meets the Two-Month Stability of the Asserted Claims

Regeneron, like the district court, improperly focuses its construction analysis on the word “stable” in reference claim 5, instead of the whole term “stable for at least 4 months.” As explained in Celltrion’s opening brief, to understand what the inventors meant when they described the formulation of claim 5 as being “stable for at least 4 months,” a POSA would have consulted the tables in Examples 3 and 4, which are the only portions of the specification that discuss the stability of the claim 5 formulation over a four-month period (or otherwise). *See generally*, Appx08286-Appx08287. The tables, which report stability testing at 5° C over a four-month period, demonstrate that at least 98% of the VEGF trap included in the claim 5 formulation remained in “native conformation” as measured by SEC at the two-month mark. The tables further reveal that the claim 5 formulation inherently possesses the storage stability of the asserted claims. Whether expressly or inherently, reference claim 5 anticipates the stability limitations of the asserted claims. Indeed, if the Court credits Celltrion’s proposed construction of

the stability limitations of the asserted claims, Regeneron has effectively conceded this anticipation.

With no other option to save the asserted claims, Regeneron focuses on contesting Celltrion's construction. Regeneron first protests that Celltrion did not advance its claim construction until its preliminary injunction sur-reply. RB 50. But Regeneron did not submit the fact declaration of Dr. Graham—in which he describes a purported sample of EYLEA of unknown age or providence in which more than 3% of the aflibercept had aggregated *prior to* storage—until it filed its reply. Nor did Regeneron articulate its contrary construction, requiring the formulation of the asserted claims to be made with aflibercept that is at least 98% pure prior to storage, until that reply, to take advantage of the late-filed Graham declaration. Further, in Regeneron's opening preliminary injunction brief, and during prosecution of the asserted claims, Regeneron represented that the stability limitation relates to “the percentage of the VEGF antagonist which maintains its conformation following storage over a given period of time.” Appx07863; Appx00588. In other words, the inhibition of the aggregation over time during storage, not initial purity. Celltrion thus had no reason to believe the

parties had a dispute as to claim construction, or assert the construction it does here, until its sur-reply.

Contrary to Regeneron's suggestion, Celltrion's construction is entirely consistent with the specification's disclosures that "preferably" "at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation." Br. 61-62 (quoting Appx00411, 6:50-55). That the VEGF trap may "preferably" be substantially free of aggregate impurities prior to storage underscores that the inventors did not view their invention as being limited to formulations made with highly-pure VEGF trap. Indeed, the specification makes no mention of the initial purity of the VEGF trap being critical to stability, and certainly not any mention that stability hinged on greater-than-98% purity. Instead, the specification indicates that the particular types and amounts of excipients, *i.e.*, buffer, organic co-solvent, stabilizing agent, salt and pH, convey the claimed stability. Br. 60-62. Regeneron's attempt to read an initial purity limitation into the asserted claims is untethered from the description of the invention in the specification and is a transparent attempt to avoid inherent anticipation by claim 5.

b. In the Alternative, a POSA Would Have Considered Obvious the Use of Highly Pure Aflibercept in Making the Invention of Claim 5

At a bare minimum, using highly purified aflibercept would have been obvious to a POSA. Celltrion's expert Dr. Tessier's opinion that in general, a POSA would want to use active ingredient that is as pure as possible when making a pharmaceutical product like EYLEA, intended for injection into the eye, stands un rebutted. Br. 63. Achieving that purity unquestionably would have required nothing more than ordinary skill, since the '594 patent does not disclose how to obtain aflibercept of any specific purity. *Id.* Obviousness requires nothing more.

Regeneron asserts that this argument was forfeited as it was raised for the first time in Celltrion's sur-reply. This, as explained, was not a situation of Celltrion's own making. Further, the court *granted* Celltrion's motion for leave to file a sur-reply and made it part of the record below. It demonstrates that Celltrion has at least a "substantial" obviousness defense to present at trial, which is all that is required to defeat a preliminary injunction motion. The district court also expressly stated that it fully considered Celltrion's obviousness argument in making its ruling, and Regeneron had a full and fair opportunity to

defend the court's analysis in its brief on appeal. Review of the court's judgment in this regard is thus appropriate in this appeal.

4. Objective Indicia Do Not Support Non-Obviousness

For all of Regeneron's posturing, the totality of objective indicia it cites speaks not to the inventive concepts of the asserted claims, of which there are none, but instead to the success of its commercial EYLEA formulation. *E.g.*, RB 3 ("In contrast to 'the many clinical failures Regeneron had experienced during its decades of existence,' '[t]he claimed composition—40 mg/ml of aflibercept, with polysorbate 20, a buffer, and a stabilizing agent'—'became the leading medicine in its class and a revolutionary treatment for treating angiogenic eye disorders.'"); *see also id.* at 6 (acknowledging that Examples 3 and 4 disclose a liquid formulation having the same components as EYLEA). According to Regeneron, "Eylea's 'captivating' combination of properties that were appreciated only after the invention of the claimed formulations and thus were not disclosed in the specification." RB 61. But what Regeneron fails to acknowledge is that its commercial EYLEA formulation is exactly the same as the formulation described in reference claim 5. In fact, reference claim 5 is closer to the commercial formulation because, unlike the

asserted claims, it specifies the type and amount of each excipient in EYLEA. Br. 10. Objective indicia thus cannot support a finding of non-obviousness.

II. Regeneron Failed To Demonstrate That It Likely Has Personal Jurisdiction Over Celltrion

Regeneron contends that personal jurisdiction over Celltrion Inc. in West Virginia is proper solely because Celltrion submitted an aBLA and purportedly did not deny that its U.S. distributor may market in West Virginia. RB 62-63. If accepted, Regeneron's personal jurisdiction theory would upend decades of Supreme Court and Federal Circuit precedent and subject all foreign generic filers to suit anywhere in the United States. But *Acorda Therapeutics v. Mylan Pharmaceuticals*, 817 F.3d 755 (Fed. Cir. 2016) is not that sweeping, and Regeneron fails to substantively address the "other considerations" that *Acorda* mandates or the lack of minimum contacts raised in Celltrion's opening brief, both of which distinguish this case from *Acorda*. Br. 66-68.

As to the former, Regeneron cites nothing to support its assertion that litigating in West Virginia poses no burden on Celltrion. RB 65. Of course it does. Celltrion has no contacts in West Virginia. There is no dispute that, unlike in *Acorda*, Celltrion is not licensed to do business in

West Virginia, has no office or registered agent in West Virginia, and has never litigated there. *See id.*

Reversing on personal jurisdiction would also not be a “Pyrrhic” victory. As noted by Samsung (*Regeneron Pharms., Inc. v. Mylan Pharms., Inc.*, No. 24-1965, ECF No. 43 at 12 (Sept. 16, 2024)) and Formycon (*Regeneron Pharms., Inc. v. Mylan Pharms., Inc.*, No. 24-2009, ECF No. 34 at 2 n.1 (Sept. 17, 2024)), there are significant consequences to dismissal; it is not a hollow determination. If nothing else, it would vindicate Celltrion’s constitutional rights and the legal limits on the district court’s authority. The Court should reverse the district court’s contrary finding.

III. Regeneron Failed To Prove Nexus

The district court also erred in finding a nexus between Celltrion’s alleged infringement and purported irreparable harm to Regeneron. RB 68-71. This is an independent ground for reversal. Regeneron’s contrary arguments are unpersuasive.

First, there is nothing “novel” about insisting that Regeneron satisfy the demand test to obtain the extraordinary relief it seeks. Where nexus is not apparent, the demand test should be applied. Nexus can

only be “apparent” where the “infringing product contains no feature relevant to consumers’ purchasing decisions other than what the patent claims.” *Genband US LLC v. Metaswitch Networks Corp.*, 861 F.3d 1378, 1384 n.2 (Fed. Cir. 2017) (cited in RB 67 and in Appx00163-Appx00164, Appx00167). That is not the case here. While Regeneron asserts that CT-P42 “contains no such additional features,” (RB 72), undisputed evidence, including Regeneron’s own testimony that a dosing regimen drives demand, shows this is wrong. Appx13196-Appx13198 (quoting Appx14240-Appx14244).

The Court should reject Regeneron’s sweeping bid to qualify *all* pharmaceutical patents as having an “apparent nexus” in an irreparable harm inquiry. *See* RB 67-68. If that became law, a patentee like Regeneron, willing to invest in thickets of overlapping formulation patents claiming only trivial differences from expired patents, would never have to tie harm from infringement to those trivial differences. Because injunctions are extraordinary remedies not to be routinely granted, (*Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir. 1993)), there is no compelling reason to exempt pharmaceutical patentees from proving this harm.

Second, Regeneron cannot meet the demand test when properly applied. Regeneron has not proven that the claimed features of the '865 patent—as opposed to the features of EYLEA in now-expired reference claim 5 or in other patents—drive demand for EYLEA. The district court found that “safety, efficacy, and opportunities for extended dosing intervals” were due to the '865 patent (RB 70-71), but the court premised this finding entirely on the *Mylan* decision, which was founded on the 40 mg/ml and intravitreal elements that are also present in now-expired reference claim 5. Appx00171-Appx00172. Regeneron disagrees, but points to no support in this record.

Regeneron protests that it could not be expected to prove that the asserted claims' unique limitations (e.g., RB 69)—rather than the claimed invention as a whole—drives demand. But no matter the level of generality, Regeneron has the same failure of proof. While Regeneron cites Celltrion's expert testimony that safety and efficacy considerations determine drug selection (RB 70), that testimony makes clear that those properties are due to the active ingredient aflibercept (Appx13145), which is no longer under is patent protection (Appx13194 (citing Appx13315-Appx13316)), not any aspect of the invention claimed here.

Regeneron also accuses Celltrion of mischaracterizing Dr. Trout's testimony that 95% purity may suffice for FDA approval. RB 70. But Regeneron does not explain why this is wrong, and that is the inescapable conclusion to be drawn from his testimony.

Finally, even if the appropriate question was whether Celltrion could make a non-infringing aflibercept biosimilar, the district court still erred. 95% stability may suffice for regulatory approval but does not infringe. And FDA has now approved Amgen's aflibercept biosimilar (Amgen, PAVBLU Prescribing Information (Aug. 2024), *available at* <https://tinyurl.com/5bnzzcbw>)), which the district court held did not infringe the '865 patent (*Regeneron Pharms., Inc. v. Amgen Inc.*, Case No. 1:23-CV-39-TSK-JPM, ECF No. 263 at 81 (Oct. 1, 2024)), and the district court has denied Regeneron's motion for a preliminary injunction against Amgen's launch on the ground that Regeneron *failed to prove infringement*. This is real-world proof positive that the district court's conclusion here was wrong.

CONCLUSION

For the foregoing reasons, and those stated in the opening brief, the preliminary injunction order should be reversed.

Dated: October 31, 2024

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This motion complies with the type-volume limitations of the Federal Rules of Appellate Procedure and Federal Circuit Rules because it contains 6,950 words, excluding the parts of the brief exempted by the Rules, as determined by the word-counting feature of Microsoft Word.

This brief complies with the typeface requirements because it has been prepared in a proportionally spaced typeface using Microsoft Word in Century Schoolbook 14-point font.

Dated: October 31, 2024

/s/ Robert V. Cerwinski
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CERTIFICATE OF SERVICE

I hereby certify that on October 31, 2024, I electronically filed the foregoing Brief with the Clerk of the Court using the CM/ECF system, which will send a notification of electronic filing to all counsel of record who are registered CM/ECF users.

Dated: October 31, 2024

/s/ Robert V. Cerwinski

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