

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

APPELLANT'S OPENING BRIEF

Robert V. Cerwinski
Lora M. Green
Michael B. Cottler
Aviv A. Zalcenstein
GEMINI LAW LLP
40 W 24th Street,
Suite 6N
New York, NY 10010
(917) 915-8832
rcerwinski@geminilaw.com

Jonathan Y. Ellis
Corinne S. Hockman
MCGUIREWOODS LLP
501 Fayetteville Street
Suite 500
Raleigh, NC 27601
(919) 755-6688
jellis@mcguirewoods.com

Michael Johnson
Matthew Freimuth
WILLKIE FARR &
GALLAGHER LLP
787 Seventh Avenue
New York, NY 10019
(212) 728-8127
mjohnson1@willkie.com

Counsel for Defendant-Appellant Celltrion, Inc.

PATENT CLAIMS AT ISSUE

This appeal concerns claims 4, 7, 9, 11, 14-17, 29, 32, 34, 36 and 39-42 of U.S. Patent No. 11,084,865. Claim 4 is representative of claims 4, 7, 9, 11 and 14-17:

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
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.
2. The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg /m l, and wherein said organic cosolvent comprises polysorbate.
4. The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

Appx000418, 19:29-47. Claim 4 is also representative of claims 29, 32, 34, 36 and 39-42 except that they claim a “pre-filled syringe” instead of a “vial.” Appx00418-00419.

CERTIFICATE OF INTEREST

Counsel for Celltrion, Inc. certify under Federal Circuit Rule 47.4 that the following information is accurate and complete to the best of their knowledge:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case.

Celltrion, Inc.

2. **Real Parties in Interest.** Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

None.

3. **Parent Corporations and Stockholders.** Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

Celltrion, Inc. has no parent corporation. No entity holds 10% or more stock of Celltrion, Inc.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court.

GEMINI LAW LLP: David Kim, Brigid Morris, Kyle Musgrove, Cindy Chang

WILLKIE FARR & GALLAGHER LLP: Dan Constantinescu, Ocean Lu

HISSAM FORMAN DONOVAN RITCHIE PLLC: Max C. Gottlieb,
Michael B. Hissam, Andrew C. Robey, Carl W. Shaffer

5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

[see list below]

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees).

Not applicable.

Dated: September 7, 2024

/s/ Robert V. Cerwinski
Robert V. Cerwinski

TABLE OF CONTENTS

	Page
PATENT CLAIMS AT ISSUE.....	ii
CERTIFICATE OF INTEREST	iii
TABLE OF AUTHORITIES.....	viii
STATEMENT OF RELATED CASES	xii
INTRODUCTION.....	1
JURISDICTIONAL STATEMENT	6
STATEMENT OF THE ISSUES.....	6
STATEMENT OF THE CASE	8
I. Regeneron’s Development and Patenting of a Stable Formulation of Aflibercept	8
A. The ’594 Patent	10
B. The ’865 Patent	14
C. This Patent Infringement Action.....	17
1. Regeneron initiates this multi-district litigation against its biosimilar competitors	18
2. The district court preliminarily enjoins Celltrion from launching its biosimilar	19
SUMMARY OF THE ARGUMENT	22
STANDARD OF REVIEW.....	25
ARGUMENT	25
I. The District Court’s Opinion Warrants Careful Scrutiny.....	26
II. The District Court Erred in Holding that Regeneron Is Likely to Succeed on the Validity of the ’865 Patent.....	27
A. The District Court Erred in Holding That the ’594 Patent Is not a Proper Reference Patent.....	28

1.	A terminal disclaimer re-defines the 20-year statutory patent term set by 35 U.S.C. § 154(a)	28
2.	The district court misconstrued the case law in reaching its erroneous conclusion that the '594 patent is not a proper reference patent	32
3.	The district court's holding would render terminal disclaimers meaningless and create chaos for patent expiration dates	33
4.	Regeneron's attempt to gain a six-year extension of patent term for the EYLEA formulation is exactly the kind of gamesmanship ODP is intended to bar	34
B.	Celltrion Has Raised at Least a Substantial Question of Whether the Asserted Claims of the '865 Patent Are Patentably Distinct from Claim 5 of the '594 Patent	35
1.	The trivial act of placing the claim 5 formulation in a pharmaceutical vial instead of a PFS cannot justify six more years of patent exclusivity	37
2.	The known fact that aflibercept is a glycoprotein does not render the '865 patent claims patentably distinct.....	39
3.	Describing the inherent stability of the reference claim 5 formulation in the '865 patent claims does not render them patentably distinct.....	56
4.	pH does not distinguish reference claim 5 from the asserted claims.....	64
5.	Objective Indicia Do Not Support Patentability	65
III.	The District Court Erred in Holding that It Likely Has Personal Jurisdiction Over Celltrion.....	66

IV. The District Court Erred in Finding a Nexus Between Celltrion’s Alleged Infringement and The Purported Harm to Regeneron	68
CONCLUSION	71

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>AbbVie Inc. v. Mathilda and Terence Kennedy Inst. Of Rheumatology Trust</i> , 764 F.3d 1366 (Fed. Cir. 2014)	<i>passim</i>
<i>Acorda Therapeutics Inc. v. Mylan Pharms. Inc.</i> , 817 F.3d 755 (Fed. Cir. 2016)	<i>passim</i>
<i>Allergan USA, Inc. v. MSN Lab’s Priv. Ltd.</i> , No. 2024-1061, 2024 WL 3763599 (Fed. Cir. Aug. 13, 2024).....	28, 31, 32
<i>Anderson v. City of Bessemer City</i> , 470 U.S. 564 (1985).....	27
<i>Apple Inc. v. Samsung Elecs. Co. Ltd.</i> , 735 F.3d 1352 (Fed. Cir. 2013)	24, 69, 72
<i>Arctic Cat Inc. v. Bombardier Rec. Prods. Inc.</i> , 876 F.3d 1350 (Fed. Cir. 2017)	51
<i>Atlas Powder Co. v. Ireco Chemicals</i> , 773 F.2d 1230 (Fed. Cir. 1985)	53
<i>Avocent Huntsville Corp. v. Aten Int’l Co.</i> , 552 F.3d 1324 (Fed. Cir. 2008)	69
<i>In re Basell Poliolefine Italia S.P.A.</i> , 547 F.3d 1371 (Fed. Cir. 2008)	46
<i>Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.</i> , 713 F.3d 1369 (Fed. Cir. 2013)	66
<i>Bayer Pharma AG v. Watson Labs., Inc.</i> , 874 F.3d 1316 (Fed. Cir. 2017)	51, 54

<i>Bristol-Meyers Squibb Co. v. Teva Pharms. USA, Inc.</i> , 752 F.3d 967 (Fed. Cir. 2014)	66
<i>Bristol-Myers Squibb Co. v. Superior Court of Cal.</i> , 582 U.S. 255 (2017).....	69
<i>DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.</i> , 464 F.3d 1356 (Fed. Cir. 2006)	37
<i>In re Collect, LLC</i> , 81 F.4th 1216 (Fed. Cir. 2024).....	30, 34
<i>Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.</i> , 845 F.3d 1357 (Fed. Cir. 2017)	43
<i>Entegris, Inc. v. Pall Corp.</i> , 490 F.3d 1340 (Fed. Cir. 2007)	26
<i>Galderma Labs, L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	51
<i>Genband US LLC v. Metaswitch Networks Corp.</i> , 861 F.3d 1378 (Fed. Cir. 2017)	70
<i>Genentech, Inc. v. Immunex Rhode Island Corp.</i> , 964 F.3d 1109 (Fed. Cir. 2020)	68
<i>Genentech, Inc. v. Novo Nordisk A/S</i> , 108 F.3d 1361 (Fed. Cir. 1997)	25, 26
<i>Geneva Pharm., Inc. v. GlaxoSmithKline PLC</i> , 349 F.3d 1373 (Fed. Cir. 2003)	65
<i>Gilead Sciences, Inc. v. Natco Pharma Ltd.</i> , 753 F.3d 1208 (Fed. Cir. 2014)	27, 28
<i>Golden Blount v. Robert H. Peterson Co.</i> , 438 F.3d 1354 (Fed. Cir. 2006)	27
<i>In re Gurley</i> , 27 F.3d 551 (Fed. Cir. 1994)	38

<i>H.H. Robertson, Co. v. United Steel Deck, Inc.</i> , 820 F.2d 384 (Fed. Cir. 1987)	53
<i>Inpro II Licensing, S.A.R.L. v. T-Mobile USA, Inc.</i> , 450 F.3d 1350 (Fed. Cir. 2006)	44
<i>Intel Corp. v. ULSI Sys. Tech., Inc.</i> , 995 F.2d 1566 (Fed. Cir. 1993)	25, 26
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	37, 38
<i>In re Longi</i> , 759 F.2d 887 (Fed. Cir. 1985)	27, 33
<i>Merck Sharp & Dohme Corp. v. Teva Pharm. USA, Inc.</i> , 217 F. Supp. 3d 782 (D. Del. 2016).....	32
<i>Multiform Desiccants, Inc. v. Medzam, Ltd.</i> , 133 F.3d 1473 (Fed. Cir. 1998)	43, 44
<i>Mylan Pharms., Inc. v. Thompson</i> , 268 F.3d 1323 (Fed. Cir. 2001)	25
<i>Novartis AG v. Ezra Ventures, LLC</i> , 909 F.3d 1367 (Fed. Cir. 2018)	30
<i>In re Petering</i> , 301 F.2d 676 (C.C.P.A. 1962).....	44, 45
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	39, 41
<i>In re Samuels</i> , No. 2021-2166, 2024 WL 960453 (Fed. Cir. Mar. 6, 2024).....	50
<i>Titanium Metals Corp. of Am, v. Banner</i> , 778 F.2d 775 (Fed. Cir. 1985)	44
<i>Vitrionics Corp. v. Conceptronic, Inc.</i> , 90 F.3d 1576 (Fed. Cir. 1996)	40

<i>World-Wide Volkswagen Corp. v. Woodson</i> , 444 U.S. 286 (1980)	69
--	----

<i>In re Yamazaki</i> , 702 F.3d 1327 (Fed. Cir. 2012)	29, 33
---	--------

Statutes

28 U.S.C. § 1292(c)(1)	6
28 U.S.C. § 1338	6
28 U.S.C. § 1407	19
35 U.S.C. § 271(b), (c), (e)	18
35 U.S.C. § 154(a)	<i>passim</i>
35 U.S.C. § 154(b)	30
35 U.S.C. § 156	30, 32
35 U.S.C. § 253(a)	30
42 U.S.C. § 262(l)(3)	17
42 U.S.C. § 262(l)(6)	18
42 U.S.C. § 262(l)(8)(A)	17

Other Authorities

Manual of Patent Examining Procedure (9th Ed., 2022)	31, 33
--	--------

STATEMENT OF RELATED CASES

The following cases may directly affect or be directly affected by this Court's decision in the pending appeal:

- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2002 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2009 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2019 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2058 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2082 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 24-2083 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Nos. 23-1395, -1396 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Nos. 24-1402, -1405 (Fed. Cir.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Nos. 24-1564, -1567 (Fed. Cir.)
- *In re: Aflibercept Patent Litigation*, No. 1:24-md-3103 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 2:24-cv-264 (C.D. Cal.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 1:24-cv-39 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-106 (N.D.W. Va.)

- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-94 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Formycon AG*, No. 1:23-cv-97 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:23-cv-89 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:24-cv-53 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 1:22-cv-61 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Sandoz Inc.*, No. 3:24-cv-08760 (D.N.J.)
- *Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00442 (P.T.A.B.)
- *Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00739 (P.T.A.B.)
- *Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2024-00201 (P.T.A.B.)
- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 (P.T.A.B.)
- *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-00258 (P.T.A.B.)
- *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-00298 (P.T.A.B.)
- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00880 (P.T.A.B.)
- *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-00257 (P.T.A.B.)

- *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-00301 (P.T.A.B.)
- *Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00884 (P.T.A.B.)
- *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2024-00260 (P.T.A.B.)
- *Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2024-00298 (P.T.A.B.)
- *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-01524 (P.T.A.B.)
- *Mylan Pharmaceuticals, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00099 (P.T.A.B.)
- *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, PGR2021-00035 (P.T.A.B.)

INTRODUCTION

This appeal involves a simple, straightforward case of obviousness-type double patenting (“ODP”). Nearly 30 years ago, Regeneron developed aflibercept, a glycoprotein that inhibits the action of a signaling protein known as vascular endothelial growth factor (“VEGF”), which, when over-expressed in the retina, can damage the retina and cause vision loss. By inhibiting the activity of VEGF, aflibercept can reduce or reverse such vision loss when injected into the eye. The original patents Regeneron received for discovering aflibercept and its use as a VEGF inhibitor have long since expired.

In the early 2000’s, Regeneron devised a pharmaceutical formulation with aflibercept sufficiently concentrated to fit into the small volumes typically injected into the eye, but also sufficiently shelf-stable to be a practical pharmaceutical product. Regeneron now sells this formulation in vials and pre-filled syringes under the trade name EYLEA. Regeneron’s U.S. Patent 9,340,594 covers the EYLEA formulation. As a result of terminal disclaimers, that patent has also expired—more than three years ago.

With these primary patent barriers removed and Regeneron's regulatory exclusivity expired, Celltrion and other manufacturers sought regulatory approval to market less expensive, biosimilar versions of EYLEA. That is how the system is designed to work. Regeneron was afforded the full term of its exclusive right to profit from the sale of its EYLEA formulation—in accord with the terminal disclaimers it voluntarily agreed to—enabling Regeneron to recoup its investment and earn many billions of dollars in profits. Now, it is the public's turn to get access to EYLEA at affordable prices as the benefit of its patent bargain with Regeneron.

Yet in a bid to extend the term of its patent protection for EYLEA, Regeneron filed a later patent application sharing a common specification with the '594 patent covering the EYLEA formulation. That patent, U.S. Patent 11,084,865, does not expire until June 14, 2027, *more than six years after the '594 patent's expiration*. By omnibus proceedings brought against all manufacturers seeking marketing approval for biosimilar versions of EYLEA, Regeneron has interposed the '865 patent as the sole patent barrier preventing patients from accessing these lower-cost, biosimilar products.

This appeal concerns the district court's preliminary injunction barring Celltrion from launching its lower-cost biosimilar version of EYLEA based on alleged infringement of the '865 patent. In opposing that preliminary injunction, Celltrion presented preliminary—but conclusive—evidence that Regeneron's later-filed, later-issued, and later-expiring '865 patent is invalid for ODP over claim 5 of the '594 patent.

The district court critically erred in finding that Regeneron is likely to succeed in the face of Celltrion's ODP invalidity challenge. The earlier-issued, earlier-expiring, and commonly owned '594 patent is a proper reference patent to the '865 patent. And there is no patentable distinction between reference claim 5 of the '594 patent and the asserted claims. The relevant claims all teach essentially the same formulation of aflibercept with the same inherent stability. The limitations that Regeneron added to the '865 patent to overcome the PTO's initial (and correct) ODP rejection are nothing more than re-worded descriptions of that formulation's inherent features. To the extent the Court credits the district court's view that there are differences, those differences would have been trivially obvious.

The district court failed to acknowledge ODP invalidity via four principal legal errors. *First*, it rejected the '594 patent as a proper reference patent by ignoring the effect of Regeneron's terminal disclaimer on the patent's statutory term. The court's view that terminal disclaimers do not modify a patent's term, but merely render some portion of it "unenforceable," is irreconcilable with this Court's precedent and would vitiate the utility of terminal disclaimers. *Second*, the district court improperly construed—or failed to construe—the key terms of the reference and asserted claims, and in particular, failed to properly consult the common specification and prosecution history in construing their meanings and scope. This flawed claim construction analysis prevented the court from properly assessing the differences between the claims as required for an ODP analysis. *Third*, the district court failed to use the patents' common specification to gauge whether the purported differences between the claims were patentable, as this Court has repeatedly instructed analyze ODP. *And fourth*, in adjudicating obviousness, the district court did not properly apply the law of "teaching away," failing to weigh purported instances of teaching away against the prior art as a whole and improperly crediting cherry-picked, vague

statements supposedly expressing preferences for alternative VEGF antagonists as teachings that aflibercept would not be useful in the claimed formulations.

Celltrion’s biosimilar competitors—Samsung Bioepis and Formycon—have likewise appealed the district court’s parallel rulings in their respective cases, which concern other biosimilar versions of EYLEA, the same patent-at-issue, and some overlapping issues. Importantly, Celltrion’s appeal reflects evidence and arguments not in the other appeals. Principally, in contrast to Samsung and Formycon, Celltrion’s ODP analysis centers on the district court’s erroneous or absent claim constructions, failure to properly utilize the common specification to gauge anticipation and obviousness, and misapplication of “teaching away” principles, which underpin the court’s findings. Thus, while the appeals involve common issues, Celltrion’s arguments merit separate consideration.

For these reasons and those explained more fully below, the Court should reverse.

JURISDICTIONAL STATEMENT

The district court has subject matter jurisdiction over the patent action under 28 U.S.C. § 1338. This Court has jurisdiction over the appeal under 28 U.S.C. § 1292(c)(1). Celltrion filed a timely notice of appeal on July 8, 2024, ten days after the district court issued its *Order Granting Motion For Preliminary Injunction*. No. 24-2058, D.I. 1-2, at 1. Celltrion filed a second notice of appeal on July 12, 2024, two days after the district court entered its *Order for Injunctive Relief Against Celltrion*, to safeguard the effectiveness of its notice. No. 24-2147, D.I. 1-2, at 1. Celltrion's appeals were consolidated on September 3, 2024. No. 24-2058, D.I. 23; No. 24-2147, D.I. 11.

STATEMENT OF THE ISSUES

1. Whether the district court erred in finding Celltrion did not raise a "substantial question" that the asserted claims of '865 patent are invalid for ODP over reference claim 5 of the '594 patent, notwithstanding the fact that the claims of both patents cover the

formulation of Examples 3 and 4 in the common specification, which is Regeneron's commercial EYLEA formulation.

2. Whether the district court erred in finding that it could exercise personal jurisdiction over Celltrion, a foreign corporation, based on an interpretation of *Acorda Therapeutics Inc. v. Mylan Pharms. Inc.*, 817 F.3d 755 (Fed. Cir. 2016), that would indiscriminately subject pharmaceutical manufacturers to personal jurisdiction in every state regardless of the manufacturer's contacts with a forum state.

3. Whether the district court erred in concluding that Regeneron met its burden to show a nexus connecting the economic harm it would allegedly suffer from pre-trial sales of Celltrion's biosimilar with the allegedly patentable differences between the asserted claims and reference claim 5—where Regeneron presented no evidence tying product demand to those purportedly patentable differences and failed to establish that Celltrion could not manufacture its proposed biosimilar without infringing the asserted claims.

STATEMENT OF THE CASE

I. Regeneron's Development and Patenting of a Stable Formulation of Aflibercept

Aflibercept, a glycoprotein (a protein that has sugar moieties bound to it) that inhibits the action of a signaling protein known as VEGF, which, when over-expressed in the retina, can damage the retina and cause vision loss. By inhibiting the activity of VEGF, aflibercept and competing VEGF inhibitors such as bevacizumab and ranibizumab can reduce or reverse such vision loss when injected into the eye. Appx10644-10674 ¶¶57-123.¹

In the early 2000's, Regeneron devised a particular 40 mg/ml pharmaceutical formulation of aflibercept that was sufficiently concentrated and shelf-stable to be approved and marketed as an intravitreal injectable product. Regeneron eventually commercialized this formulation under the trade name EYLEA, in both vial and pre-filled syringe ("PFS") formats. *See, e.g.*, Appx0006 (citing Appx01273-01274 ¶48). EYLEA contains 40 mg/ml of aflibercept, 40 mM NaCl, 0.03%

¹ Celltrion's ODP arguments are supported by the expert opinions of Peter M. Tessier, Ph.D., a professor and industry consultant with extensive experience in biologic formulations. Appx00018; Appx10630-10634 ¶¶1, 2, 5, 10-18; Appx10766-10776.

polysorbate 20, 10 mM phosphate, 5% sucrose, and has a pH of approximately 6.3. Appx10678-10679 ¶¶149-52. EYLEA is administered via intravitreal injection and approved for the treatment of various eye diseases mediated by VEGF. Regeneron's regulatory exclusivity for EYLEA expired on May 18, 2024. Appx00013.

Soon after developing EYLEA, Regeneron initiated a “patent thicket” strategy to protect it from biosimilar competition.² Over a span of almost two decades, Regeneron filed several original patent applications covering formulations of aflibercept having the same combination of buffer, organic co-solvent, and sugar stabilizer, and thereafter, a blizzard of divisional and continuation applications that claimed various permutations of this same combination of excipients, using a variety of different claim structures. The fruit of this strategy

² Patent thickets covering branded biologics are a growing problem in the U.S. This strategy involves obtaining multiple duplicative patents driving up the cost of challenging those patents. Many in industry and government have bemoaned this problem as driving up the cost of prescriptions. *See, e.g.*, Appx16920-16924. In response, legislators have proposed bills to mitigate a patentee's ability to assemble or enforce such thickets. *See, e.g.*, Appx16931-16937. But a legislative fix has eluded Congress.

was the issuance of dozens of patents with overlapping claims to the same basic formulation.

To obtain these duplicative patents, Regeneron had to overcome repeated ODP rejections by the PTO. Regeneron did so by voluntarily filing terminal disclaimers in almost all the applications. As a result, almost all the patents in the thicket have now expired.

A. The '594 Patent

One now-expired patent in Regeneron's thicket, the '594 patent, is central to this appeal. Claim 5 of this patent is a "picture" claim to the particular combination of ingredients that constitute EYLEA, disposed within a PFS. It is directed to a "pre-filled syringe suitable for intravitreal administration" containing a "stable ophthalmic formulation" comprising the same ingredients as EYLEA: 10 mM phosphate at a pH of 6.2-6.4, 40 mM sodium chloride, 0.03% polysorbate 20, 5% sucrose, and 40 mg/ml of "VEGF trap" protein. Appx08292, 20:21-24. The patent also discloses this same formulation disposed within a glass vial. Appx08286-08287, Example 3.

Claim 5 specifies that the "VEGF trap" consists of "amino acids 27-457 of SEQ ID NO:4," which is the amino acid sequence of aflibercept.

The specification mentions this particular “VEGF trap” only once, describing it as a “specific embodiment” in which the “fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn [asparagine] residues 62, 94, 149, 222 and 308.” Appx08285, 6:4-7.

Claim 5, through its dependencies on claims 3 and 4, further specifies that the formulation’s ingredients cause the aflibercept to be “stable for at least 4 months.” Appx08292, 19:38-39. The only description of this stability is in Examples 3 and 4. In these examples, samples of the claim 5 formulation were stored at 5° C and “tested at 0.5, 1, 2, 3, and 4 months” for the formation of aggregates and particulates by size-exclusion chromatography (“SEC”) and measurements of turbidity. SEC and turbidity measurements can detect the formation of aggregates and particulates in a sample of protein. *See* Appx10670-10673 ¶¶117-21. The results in Table 3 of Example 3 for samples stored in vials show little formation of aggregates over the four-month storage period:

TABLE 3

Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)					
Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.5
0.5	Pass	0.00	6.3	99	99.4
1	Pass	0.00	6.2	98	99.5
2	Pass	0.00	6.2	95	99.2
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

Appx08287, 9:1-13. The results in Table 4 of Example 4 for samples stored in PFS are nearly identical to those of Table 3:

TABLE 4

Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)					
Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.4
0.5	Pass	0.00	6.3	100	99.3
1	Pass	0.00	6.3	100	99.4
2	Pass	0.00	6.3	97	99.1
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

Appx08287, 9:31-43.

Tables 3 and 4, like all of the tables, refer to aflibercept as “VEGF Trap Protein.” Examples 3 and 4, like all of the examples, refer to aflibercept as “VEGF trap (SEQ ID NO:4).” Regeneron’s expert, Dr. Trout, conceded below that a person of ordinary skill in the art (“POSA”)

would have understood from the specification that the protein referred to as “VEGF trap” in the tables and examples was the “specific embodiment” referred to in the specification as the “fusion protein compris[ing] amino acids 27-457 of SEQ ID NO:4 and [that] is glycosylated at Asn [asparagine] residues 62, 94, 149, 222 and 308.” *See* Appx10687 ¶170 (citing Appx12761-12769, 154:1-162:4; Appx12781-12782, 174:11-175:7).

Regeneron filed the ’594 patent in 2014 as a continuation of a series of applications within a “family” wherein the first utility application was filed June 14, 2007. The examiner initially maintained a rejection for ODP over Regeneron’s U.S. Patent No. 7,608,261. *See* Appx10687 ¶169 (citing Appx12586). The ’261 patent is part of the same family as the ’594 patent, but Regeneron had terminally disclaimed it over a Regeneron patent from a different family, U.S. Patent No. 7,531,173, which Regeneron had terminally disclaimed over a Regeneron patent from a third family, U.S. Patent 7,374,757. To secure allowance of the ’594 patent over these earlier-issued patents within Regeneron’s thicket, Regeneron again agreed to a terminal disclaimer. *See* Appx15490. As a result, the ’594 patent issued on May 17, 2016, but expired on March 7,

2021—three years *before* the end of Regeneron’s regulatory exclusivity. Appx15505.

B. The ’865 Patent

As the ’594 patent’s expiration date approached, in a bid to extend its patent protection, Regeneron filed a later continuation application covering the same EYLEA formulation on January 10, 2020. As with the ’594 patent, the PTO initially rejected the claims of the ’865 patent for ODP, this time over the ’594 patent and three other, later-expiring Regeneron patents Regeneron had accrued since the ’594 patent issued, U.S. Patents 8,092,803, 7,608,261 and 9,914,763. Appx07857-07859. But this time Regeneron declined to file a terminal disclaimer over the ’594 patent, which would have defeated the utility of Regeneron’s new patent filing.

Instead, Regeneron added claim elements drawn to two properties of EYLEA not expressly mentioned in the claims of the ’594 patent: (1) the fact that aflibercept is a glycoprotein, and (2) the reported stability imparted by the ingredients of the EYLEA formulation when stored for two or twenty-four months under the conditions of Examples 3 and 4.

Some of the claims were also drawn to EYLEA placed in a vial instead of a PFS.

With respect to glycosylation, Regeneron maintained the requirement that the “VEGF antagonist fusion protein” be aflibercept, *i.e.*, comprise “amino acids 27-457 of SEQ ID NO:4,” but added the element “wherein said VEGF antagonist fusion protein *is glycosylated*,” which was a known property of aflibercept disclosed in the specification and prior art. Appx07867. It also added dependent claims describing the known glycan structure of aflibercept, *i.e.*, “wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO:4.” *See* Appx00418-00419 claims 14, 39.

With respect to stability, Regeneron added the element to the independent claims “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,” which is a description of the stability test data reported in Examples 3 and 4. Appx07867. Regeneron also added dependent claims reciting additional data reported in Examples 3 and 4, including that the formulation “is capable of

providing a turbidity of 0.01 or lower at OD₄₀₅ after 2 months storage at 5° C,” *see* Appx00419, claim 40, and that “at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 months storage at 5° C, as measured by SEC.” *See* Appx00419, claim 41. Regeneron also added dependent claims reciting 24-month stability test data for the non-EYLEA formulations reported in Examples 1 and 2, *i.e.*, that “at least 98% of said VEGF antagonist fusion protein is present in native conformation after 24 months storage at 5° C, as measured by SEC.” *See* Appx00419, claim 42. Regeneron presented two identical sets of claims with all of these recitations, one set directed to the formulation disposed within a “vial,” and the other set to a PFS. *Compare* Appx00418-00419, claims 1-25 *with* claims 26-50.

Regeneron asked the examiner to reconsider and withdraw its ODP rejection in light of the amended claims. Appx07861-07863. Notably, Regeneron did not draw the examiner’s attention to the fact that the amended claims covered the same formulation claimed in the ’594 patent and tested in Examples 3 and 4, or that the amended stability limitations were essentially a description of the results of those examples. Nor did it draw the examiner’s attention to the fact that Regeneron had fully

disclosed the glycoprotein structure of aflibercept in *Daly*, a prior art, published Regeneron patent application.

The examiner allowed the claims and issued the '865 patent on August 10, 2021. Appx07868. This later-filed, later-issued patent to EYLEA expires on June 14, 2027, more than six years after the expiration of the '594 patent.

C. This Patent Infringement Action

In June 2023, Celltrion filed Biologics License Application (“BLA”) No. 761377 with the FDA, seeking approval for its CT-P42 biologic product as an interchangeable biosimilar to EYLEA. Appx00275-00276 ¶3; Appx05471. After FDA notified Celltrion that its BLA had been accepted for review, Regeneron and Celltrion engaged in the pre-suit exchange of information required by 42 U.S.C. § 262(l)(3) known as the “patent dance.” *See generally, e.g.*, Appx05438-05469. During their “dance,” Celltrion notified Regeneron under 42 U.S.C. § 262(l)(8)(A), that it may began commercial marketing immediately following approval. Appx00276 ¶4.

When Regeneron indicated its intention to block that launch with a preliminary injunction motion, Celltrion offered to discuss proper

jurisdictions for any infringement suit. Regeneron refused. *See generally* Appx00420-00437.

1. Regeneron initiates this multi-district litigation against its biosimilar competitors

While the patent dance was ongoing, Regeneron filed its first complaint against Celltrion in the Northern District of West Virginia, asserting infringement of 38 patents under 35 U.S.C. § 271(b), (c), (e), and/or (g). Appx00276-00277. Celltrion moved to dismiss the complaint for lack of personal jurisdiction, on the ground that neither it nor its distributor had the required contacts with West Virginia. Appx00446-00483. Regeneron opposed that motion. Appx00531-00564.

Once the parties completed the patent dance, Regeneron filed a second complaint, alleging infringement of 25 of the 38 patents included in its first complaint. Complaint, *Regeneron Pharms, Inc. v. Celltrion, Inc.* No. 24-cv-53, ECF No. 1 (W.D. Va. May 17, 2024); *see* 42 U.S.C. § 262(l)(6) (requiring any infringement suit to be filed within 30 days of completion of the patent dance). The parties stipulated to the dismissal of 12 patents not included in the second complaint, leaving 26 at issue, and that the parties' motion and opposition concerning dismissal would

apply equally to the second complaint. Appx00225. The district court has not ruled on Celltrion's motions.

Around the same time, Regeneron moved to establish a multi-district litigation ("MDL") for all of its EYLEA-related BPCIA patent infringement actions, and to transfer its action against Amgen, Inc. from the Central District of California to the Northern District of West Virginia under 28 U.S.C. § 1407. The Judicial Panel on Multidistrict Litigation granted the motion combining six separate actions against Amgen, Mylan/Biocon, Samsung Bioepis, and Formycon, and Celltrion. Appx00188-00230.

2. The district court preliminarily enjoins Celltrion from launching its biosimilar

Prior to initiating the MDL, Regeneron moved for a preliminary injunction to bar Celltrion's launch. Celltrion proposed to Regeneron and the court that the parties each file opening briefs and supporting declarations on the issues for which they would bear the burden of proof at trial—infringement for Regeneron and validity for Celltrion—to ensure that the parties would have a fair opportunity to address each other's evidence and arguments. Regeneron refused. The district court adopted Regeneron's proposal, in which Regeneron went first and last on

both infringement and validity, with Celltrion limited to one 25-page opposition brief. When Regeneron advanced an entirely new claim construction in its reply brief, Celltrion sought and was granted a short sur-reply to address it.

Regeneron initially asserted that Celltrion's launch of CT-P42 would infringe two patents: the '865 patent and U.S. Patent 11,793,926, directed to packaging for a PFS. Appx00484. Regeneron dropped the packaging patent—after Celltrion had devoted much of its opposition to those allegations—and narrowed its preliminary injunction motion to the following claims of the '865 patent: claims 29, 32, 34, 36, and 39-42, directed to pre-filled syringes (the “PFS Claims”), and claims 4, 7, 9, 11, and 14-17, which are the same as the PFS Claims but directed to vials (the “Vial Claims”). Appx00186-00187.

The district court scheduled a hearing for early May, but abruptly cancelled it. Appx17442. After the parties jointly requested guidance regarding the hearing, Appx17407, the court held a status conference at which it requested simultaneous submission of “proposed orders,” with no opportunity to respond or object to the other party's proposed order. Appx17522-17523. In contrast to the 25-pages allotted for the parties'

briefs, Regeneron submitted a 120-page proposed order with new and substantially expanded arguments. Appx17596-17731.

On June 28, 2024, without holding a hearing, the district court issued an order granting Regeneron's motion for a preliminary injunction. Appx00004-00185. Its order adopted—nearly verbatim—Regeneron's proposed order, including its new and expanded arguments that were not part of its briefs of record, and which relied on evidence and factual findings from Regeneron's separate action against a different competitor, Mylan, to which Celltrion was not a party. *Id.* The district court ruled that Regeneron had met its burden of establishing all four preliminary injunction factors, rejecting Celltrion's ODP defense and concluding that Regeneron would be irreparably harmed by the launch of CT-P42. Appx00046-00181. The court also concluded that Regeneron had shown a "reasonable probability of personal jurisdiction" based on Celltrion's BLA filing and relationship with its distributor. Appx00027-00035.

On July 10, 2024, the court issued a short additional order specifying the terms of the injunction. Appx00001-00003.

SUMMARY OF THE ARGUMENT

I. The district court erred in holding that Regeneron is likely to succeed on the merits of its infringement claim in the face of Celltrion’s ODP challenge to the ’865 patent.

The commonly-owned, now-expired ’594 patent is a proper reference patent against the ’865 patent because it was the first-filed, first-issued, and first-expiring patent as compared to the ’865 patent. This Court has previously rejected the district court’s ruling that terminal disclaimers do not curtail a patent’s term but merely render the disclaimed portion “unenforceable.” If affirmed, the district court’s view would render terminal disclaimers meaningless and patent expiration dates uncertain.

There is also no patentable distinction between claim 5 of the ’594 patent and the asserted claims, both of which cover Regeneron’s commercial EYLEA formulation. Merely swapping one conventional packaging for another—a vial for a PFS—cannot entitle Regeneron to a new patent for EYLEA. Nor do the glycosylation and stability limitations added to the asserted claims provide any patentable distinction. Claim 5 in fact anticipates those limitations. The specification shared by both

patents makes clear that the VEGF antagonist in claim 5 is aflibercept, a known glycoprotein, and that the claim 5 formulation has the same stability as the asserted claims, although it uses different words to describe that stability.

In reaching a contrary conclusion, the district court wrongly construed claim 5 as teaching a two-species “genus” of aflibercept and aflibercept with its glycans removed. Even if this were true, the POSA would still have envisioned intact aflibercept as a species and thus the genus still anticipates. Intact aflibercept also would have been an obvious species—and indeed the only known species—to use in the alleged genus.

The district court also wrongly construed the four-month stability of the claim 5 formulation to be different than the two-month stability of the asserted claims. But Examples 3 and 4, which report stability of the claim 5 formulation over four months, demonstrate that the claim 5 formulation has the same stability at two months as the asserted claims. The difference between the claims is semantic, not substantive.

The district court also failed to heed this Court’s guidance on when a prior-art reference “teaches away” and improperly relied on vague,

cherry-picked statements from the art cited by Regeneron to contradict the plain teachings of claim 5 and the specification, while ignoring key evidence cited by Celltrion.

II. The district court further erred in finding that it likely had jurisdiction over Celltrion. The court misinterpreted this Court's holding in *Acorda* to indiscriminately subject pharmaceutical manufacturers to personal jurisdiction in every state regardless of the manufacturer's minimum contacts with a forum state. Where, as here, a defendant has no contacts with the forum state, this interpretation of *Acorda* would trample decades of established personal jurisdiction precedent and offends due process.

III. Finally, the district court erred in concluding that Regeneron satisfied the nexus requirement for demonstrating likely irreparable harm from the asserted infringement. The court failed to apply the demand test articulated in *Apple Inc. v. Samsung Elecs. Co. Ltd.*, 735 F.3d 1352 (Fed. Cir. 2013), instead alleviating Regeneron of its burden to prove Celltrion's purported infringement of the '865 patent would drive demand for its biosimilar product. In fact, Regeneron presented no evidence tying product demand to the claimed features of the '865 patent.

STANDARD OF REVIEW

This Court reviews the decision to grant a preliminary injunction for abuse of discretion. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997). A district court abuses its discretion by granting an injunction based on an error of law or on clearly erroneous factual findings. *Id.* “To the extent that a district court’s decision to grant a preliminary injunction hinges on questions of law, [this Court’s] review is *de novo*. *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323, 1329 (Fed. Cir. 2001), *abrogated on other grounds*, *Caraco Pharm. Lab’ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012). Underlying factual determinations are reviewed for clear error. *AbbVie Inc. v. Mathilda and Terence Kennedy Inst. Of Rheumatology Trust*, 764 F.3d 1366, 1372 (Fed. Cir. 2014).

ARGUMENT

A preliminary injunction is a “drastic and extraordinary remedy that is not to be routinely granted.” *Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir. 1993). To obtain this extraordinary relief in an infringement suit, the patentee must establish (1) a likelihood of success on the merits, including that the patent is both valid and

infringed; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships favors patentee; and (4) the injunction is in the public's interest. *Id.*; *Entegris, Inc. v. Pall Corp.*, 490 F.3d 1340, 1351 (Fed. Cir. 2007). Where a defendant raises a question of validity that the patentee cannot prove “lacks substantial merit,” then “the preliminary injunction should not issue.” *Genentech*, 108 F.3d at 1364. A “substantial question” of validity is one that shows the patent is “vulnerable;” it “requires less proof than the clear and convincing showing necessary to establish invalidity” at trial. *Entegris*, 490 F.3d at 1351 (internal quotations omitted).

The district court erred in finding that Regeneron met its burden to justify such extraordinary relief here. Celltrion raised far more than a substantial question regarding whether the asserted claims are invalid for ODP over reference claim 5. Regeneron also failed to show a substantial likelihood that Celltrion is subject to personal jurisdiction in West Virginia. And Regeneron failed to connect any likely irreparable harm to the allegedly patentable features of the asserted claims. This Court should reverse.

I. The District Court’s Opinion Warrants Careful Scrutiny

At the outset, the district court’s order warrants careful scrutiny from this Court. After receiving one round of 25-page briefs on Regeneron’s motion for the preliminary injunction and canceling the scheduled hearing, the district court adopted nearly all of Regeneron’s 120-page order essentially verbatim. Celltrion had no opportunity to respond to Regeneron’s proposed order or the expanded arguments it contained. Although the wholesale adoption of Regeneron’s proposed order does not subject it to a different standard of review, this Court has noted that the practice “may result in ... close scrutiny,” which Celltrion respectfully submits is appropriate here. *See Golden Blount v. Robert H. Peterson Co.*, 438 F.3d 1354, 1359 (Fed. Cir. 2006) (citing *Anderson v. City of Bessemer City*, 470 U.S. 564, 572 (1985)).

II. The District Court Erred in Holding That Regeneron Is Likely to Succeed on the Validity of the ’865 Patent

Once a patent expires, the public has the right to use the claimed invention and its obvious variants. *See Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014). ODP protects this right by prohibiting, among other things, common inventors from obtaining a later patent containing claims that are anticipated by, or

obvious variants of, the claims of an earlier-filed, earlier-expiring “reference” patent. *See, e.g., AbbVie Inc.*, 764 F.3d at 1372-74; *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). That prohibition applies here.

A. The District Court Erred in Holding That the ’594 Patent Is not a Proper Reference Patent

The ’594 patent is a proper ODP reference against the ’865 patent. Both are members of the same patent family and are commonly owned by Regeneron. The ’865 patent was filed after the ’594 patent issued and expires more than six years later. ODP requires nothing more. *See Gilead Sciences*, 753 F.3d at 1212, 1215-16; *see also Allergan USA, Inc. v. MSN Lab’s Priv. Ltd.*, No. 2024-1061, 2024 WL 3763599, at *5-6, *8 (Fed. Cir. Aug. 13, 2024). The district court’s contrary reasoning is misguided.

1. A terminal disclaimer re-defines the 20-year statutory patent term set by 35 U.S.C. § 154(a)

The district court held that “because the [’865 patent] and the ’594 Patent share the same parent patent and have the same statutory term, the ’594 Patent cannot be an ODP reference simply because the ’594 Patent expired after a terminal disclaimer.” Appx00066-00067. The district court’s conclusion that the two patents “have the same statutory term” was founded on its belief that the effect of Regeneron’s terminal

disclaimer was merely to “render [the patent] unenforceable before the end of its statutory 20-year term” dictated by 35 U.S.C. § 154(a). Appx00068. This was legal error.

The statutory term of the ’594 patent ended on March 7, 2021, the date set for the patent when it issued. That this expiration date was set by a terminal disclaimer does not make it any less “statutory.” This Court explicitly rejected the district court’s view in *In re Yamazaki*, explaining that a terminal disclaimer does not merely render the patent unenforceable for the disclaimed period, it “redefines” the original statutory term of the patent upon issuance:

According to *Yamazaki*, a terminal disclaimer does not alter [the] statutorily defined term [under § 154(a)] but merely adjusts the patent's expiration date without altering the statutory term itself... We ... cannot agree with *Yamazaki*'s view of patent term as an absolute, immutable statutory grant under § 154(a)—patent term calculations begin but do not necessarily end with that section. Various statutory devices, *including a recorded terminal disclaimer*, can *redefine the term of an original patent*. When a patent issues subject to a terminal disclaimer, the patentee ... has not just agreed to forego some amount of enforceable term, but has in fact *reduced the term itself by effectively eliminating the disclaimed portion from the original patent*.

In re Yamazaki 702 F.3d 1327, 1331-33 (Fed. Cir. 2012) (emphasis added).

Here, the statutory term of the '594 patent was defined by two statutory devices: the 20-years-from-filing period specified by § 154(a) and the terminal disclaimer provided for by 35 U.S.C. § 253(a), which curtailed the period specified by § 154(a).

This is consistent with this Court's ODP-related holdings concerning other statutory modifications to the 20-year term specified in § 154(a). In *In re Collect, LLC*, the Court found that patent term adjustments ("PTAs") granted under 35 U.S.C. § 154(b) re-define the statutory expiration date of a patent for purposes of ODP. 81 F.4th 1216, 1226 (Fed. Cir. 2024). Similarly, in *Novartis AG v. Ezra Ventures, LLC*, the Court recognized that a patent term extension ("PTE") granted under 35 U.S.C. § 156 "is the literal changing of the patent's expiration date by the Director under § 156, ensuring a government-granted de jure exclusionary right for an extended time period" for "one patent selected by the patent owner"—even while interpreting the text of § 156 to prohibit limiting a PTE through an ODP bar or terminal disclaimer. 909 F.3d 1367, 1373-74 (Fed. Cir. 2018) ("*Ezra*").

The district court's flawed reasoning also cannot be squared with the fact that the Court has routinely undertaken ODP analyses between

two patents that share the same priority filing date. *See, e.g., Collect*, 81 F.4th at 1219 (finding ODP despite the fact that the reference and challenged patents “are all interrelated, each claiming priority from a single patent application”); *Allergan USA, Inc.*, 2024 WL 3763599, at *2, *8 (performing ODP analysis where “all three patents share a priority date”).

The district court’s position is also contrary to long-standing PTO practice mandating ODP rejections when an application presents claims that are not patentably distinct from an earlier-issued, commonly-owned, earlier-expiring patent, even when that patent claims entitlement to the same priority date. Manual of Patent Examining Procedure (9th Ed., 2022) (“MPEP”) §§ 804, 822. Indeed, not only did the PTO reject the originally-presented ’865 patent claims for ODP over the ’594 patent, as explained, but the PTO also expressly rejected the district court’s reasoning when it held that the ’594 patent was a proper ODP reference patent against Regeneron’s ’992 patent, another in the same family. *See* Appx16688-16689.

2. The district court misconstrued the case law in reaching its erroneous conclusion that the '594 patent is not a proper reference patent

The district court relied on this Court's opinion in *Ezra*, for the proposition that ODP does not apply when "related patents expired on different dates." Appx00072. As explained above, however, *Ezra* is consistent with this Court's cases concluding that statutory modifications to § 154(a), whether PTEs, PTAs, or terminal disclaimers, must be given effect when determining patent expiration dates for purposes of ODP unless the patent statute indicates otherwise, as § 156 does for PTEs. *See supra*, 30-31.

The district court's reliance on *Merck Sharp & Dohme Corp. v. Teva Pharm. USA, Inc.*, 217 F. Supp. 3d 782, (D. Del. 2016), a district court case that was never appealed, is also misplaced. *Merck* is distinguishable because it involved "the oddity" of a later-filed, later-issued continuation patent expiring before an earlier-filed, earlier-issued parent patent because of a terminal disclaimer. *Id.* at 787. As the Court recently held, it is the "first-filed, first issued patent ... that sets the maximum period of exclusivity for the claimed subject matter and any patentably indistinct variants." *Allergan*, 2024 WL 3763599, at *7. Here, the

earlier-expiring '594 patent was filed and issued before Regeneron filed the '865 patent. *Merck* is not applicable.

3. The district court's holding would render terminal disclaimers meaningless and create chaos for patent expiration dates

Adopting the district court's reasoning that a terminal disclaimer does not modify the term of a patent set by § 154(a) would be a radical departure from this Court's treatment of terminal disclaimers and gut their utility. The whole point of terminal disclaimers is to shorten the term set by § 154(a). Holding they do not in fact accomplish this would render these statutory tools meaningless and inflict chaos on complex patent estates and PTO procedures.

Affirming the district court would also deny the public the clear notice of patent term that terminal disclaimers provide. Once a patent issues with a terminal disclaimer, that disclaimer cannot be undone. *Yamazaki*, 702 F.3d at 1332-33. The public is entitled to rely on this date-certain expiration and "act on the assumption" that it may use the claimed subject matter or obvious variations thereof after the expiration date set by the disclaimer. *Longi*, 759 F.2d at 892-93; *see also* MPEP § 1490(VIII)(B) ("[P]ublic policy does not favor the restoration to the

Patent Owner of something that has been freely dedicated to the public.”).

4. Regeneron’s attempt to gain a six-year extension of patent term for the EYLEA formulation is exactly the kind of gamesmanship ODP is intended to bar

The district court also erred in reasoning that the ’865 patent’s later-expiring term was not the result of “gamesmanship.” Bad intent is not required for ODP. *See Cellect*, 81 F.4th at 1230. But the circumstances of this case are precisely those that ODP is designed to prevent. To secure allowance of the ’594 patent, Regeneron chose to file a terminal disclaimer referencing Regeneron’s ’173 and ’757 patents to address the Examiner’s ODP rejection. This choice—early patent protection for the EYLEA formulation in exchange for the public receiving the right to practice that formulation after the patent’s expiry date specified by the disclaimer—was voluntary, not a PTO mandate. After Regeneron received its benefit in this bargain, it then sought to deprive the public of its benefit by later filing the application that led to the ’865 patent for essentially the same formulation. That application had no function other than extending the patent protection already received for EYLEA. This is precisely the gamesmanship barred by ODP.

Having made the strategic choice to file the disclaimer, Regeneron now has little room to claim that referencing the '594 patent against the '865 patent somehow works an unfairness.

B. Celltrion Has Raised at Least a Substantial Question of Whether the Asserted Claims of the '865 Patent Are Patentably Distinct from Claim 5 of the '594 Patent

A proper ODP analysis involves two steps. The court first must construe the claims in the earlier- and later-expiring patents and determine any differences. The court must then determine whether those differences render the claims patentably distinct. *AbbVie*, 764 F.3d at 1374. Under that analysis, Celltrion raised at least a substantial question of whether the asserted claims of the '865 patent are invalid for ODP over the '594 patent.

Reference claim 5 of the '594 patent is directed to the EYLEA formulation. *See* Appx10677-10679 ¶¶145-52, Appx10687-10690 ¶¶171-74, Appx10702-10704 ¶¶221-25 (comparing claim 5 to EYLEA and asserted claims). EYLEA also meets all of the limitations of the asserted claims of the '865 patent, even though those claims permit some

variability in the amounts of the ingredients used and certain substitutions of commonly-used buffers, sugars, and surfactants.

The district court nevertheless found that the asserted claims differ from claim 5 in four ways: (1) claim 5 places the formulation in a PFS, while the asserted claims place the formulation in a PFS or a vial; (2) claim 5 does not mention that aflibercept is glycosylated, while the asserted claims do; (3) claim 5 describes the formulation as being “stable for at least 4 months,” while the asserted claims describe the stability of the formulation in terms of the results of the four-month stability tests in Examples 3 and 4; and (4) claim 5 refers to the formulation’s pH as being “6.2-6.4,” while some of the narrowest asserted claims describe the formulation as having a pH of “about 6.2-6.3.”

None of these differences in wording amount to a difference in substance. In concluding otherwise, the district court ignored Supreme Court precedent; failed to properly construe the claim terms relevant to its ODP analysis in light of the intrinsic evidence; failed to properly consult the common specification, alone and in combination with the

prior art; and misapplied the law concerning “teaching away.” Each purported difference between the claims is addressed below.

1. The trivial act of placing the claim 5 formulation in a pharmaceutical vial instead of a PFS cannot justify six more years of patent exclusivity

The district court’s finding that Celltrion did not raise at least a substantial question that a POSA would have regarded placing the formulation of claim 5 in a vial to be an obvious alternative to placing it in a PFS is egregious plain error and must be reversed.

The court failed to cite or consider one of the Supreme Court’s seminal cases on obviousness, *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). As *KSR* noted, “the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” *Id.* at 417; *see also DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006) (obviousness test “not only permits, but requires, consideration of common knowledge and common sense”).

It is undisputed that, at the relevant time, biological products were widely available in both vial and PFS formats, and a POSA would have known of no reason why a formulation presented in a PFS could not also be presented in a vial. Appx10704-10706 ¶¶226-32, Appx10673-10674 ¶¶122-23; Appx10724 ¶274. Regeneron's expert, Dr. Trout, acknowledged that the development of a vial presentation would in fact be less complicated than a PFS presentation. Appx05261 ¶395. Since it is undisputed that a vial was a well-known packaging option, yielding predictable results, *KSR* compels reversal of the district court. *KSR*, 550 U.S. at 416.

The district court's principal rationale for why a POSA would not have been motivated to place the formulation of claim 5 in a vial is that PFS were known to be more convenient for doctors than vials. Appx.00116-00117. But the fact that a PFS presentation may be more convenient does not teach away from the use of a known alternative like a vial, even if it may be less desirable. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The convenience of the PFS does not call into doubt the known, predictable utility of the vial.

2. The known fact that aflibercept is a glycoprotein does not render the '865 patent claims patentably distinct

The district court's analysis of the glycosylation limitations in the '865 patent is likewise flawed. Reference claim 5 claims the use of aflibercept, a glycoprotein known to be glycosylated at asparagine residues 62, 94, 149, 222, and 308. It therefore anticipates the aflibercept of the asserted claims. Claim 5 is not directed to a "genus" of glycosylated and non-glycosylated aflibercept, as the district court found. Even if it was, a POSA would have envisioned from the face of the claim, the specification, and the prior art that intact, glycosylated aflibercept was a member of the genus. And even if such recognition would have eluded the POSA, intact, glycosylated aflibercept was a known species that would have been obvious to use. Each of these points is addressed below.

a. The district court erred in construing reference claim 5 as claiming something broader than the use of aflibercept

The ODP analysis starts by construing the relevant claim terms. The specification should always be consulted to interpret "the scope and meaning" of a claim term. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005). The specification "is always highly relevant to the claim

construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Vitrionics Corp. v. Conception, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

Here, the specification makes clear that the phrase in claim 5 “wherein the VEGF antagonist consists of amino acids 27-457 of SEQ ID NO:4” refers to aflibercept, and that aflibercept is a glycoprotein that is glycosylated at asparagine residues 62, 94, 149, 222, and 308. *See* Appx10683-10686 ¶¶162-66.

The specification refers to “amino acids 27-457 of SEQ ID NO:4” only once in a passage that uses the word “and,” making clear this phrase refers to a specific embodiment of VEGF antagonist that is glycosylated at residues 62, 94, 149, 222, and 308:

A VEGF antagonist ... includes fusion proteins capable of trapping VEGF.... In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 **and** is glycosylated at Asn [asparagine] residues 62, 94, 149, 222 and 308.

Appx08285, 5:64-6. (emphasis added). This passage describes the glycoprotein structure of aflibercept. *See, e.g.*, Appx10652-10655 ¶¶80-83, Appx10663-10664 ¶103 (citing Appx07781 ¶13, Appx07788 ¶64;

Appx07790 Example 8 and ¶84; *see also* Appx10644-10648 ¶¶58-66. There is no reference in the specification to a VEGF antagonist with this sequence that is not glycosylated, or indeed to any VEGF antagonist that is not glycosylated. Appx10683-10687 ¶¶162-70.

Prosecution history is also relevant to claim construction. *See Phillips*, 415 F.3d at 1315. During prosecution of the '594 patent, Regeneron made statements consistent with reference claim 5 being limited to aflibercept. For example, when Regeneron amended its claims “to limit the VEGF trap to the amino acid sequence *consisting of*” the amino acid sequence of aflibercept, as the claim appears now, it explained that the claims were “*limited to a VEGF trap, which is structurally described at paragraphs [0003], [0007], and [0046],*” and “*restrict[ed] ... to structural embodiments of the VEGF antagonist that are particularly described in the specification as filed.*” Appx12579 (emphasis added); Appx10686-10687 ¶¶167-69. Paragraph [0046] in the application contains the passage that appears in the specification, quoted above, describing aflibercept. Appx12556. Similarly, when the examiner rejected the pending claims for ODP over Regeneron’s ’261 patent, which shares the same specification, the examiner referred to the claimed

sequence as a “specific preferred embodiment of VEGF antagonist,” citing the same description of aflibercept. Appx12586 (citing Appx08144, col. 5) (emphasis added); Appx10687 ¶169.

Turning to the extrinsic evidence of record, Celltrion and Regeneron’s experts agreed that a POSA would have understood the term “VEGF Trap (SEQ ID NO:4),” used in all the examples, as referring to aflibercept, *i.e.*, a VEGF antagonist consisting of amino acids 27-457 of SEQ ID NO:4, and glycosylated at residues 62, 94, 149, 222 and 308. Appx10687 ¶170 (citing Appx12761-12769, 154:1-162:4; Appx12781-12782, 174:11-175:7). This is because the only VEGF antagonist disclosed in the specification is aflibercept.

Indeed, reference claim 5 is supported by the written description in the specification only to the extent is it is glycosylated at residues 62, 94, 149, 222, and 308 and has the stability set forth in Table 4. The premise of Regeneron’s formulation patents, which recite nothing more than a combination of conventional excipients, is that stabilizing formulations of VEGF antagonist with these ingredients is an unpredictable art. It is undisputed that stripping aflibercept of its glycans could alter its stability in unpredictable ways. Appx10709-10710 ¶¶240-42 (citing

Appx12411); Appx10687 ¶170. The only formulations assessed for stability in the common specification were made with aflibercept. Appx00412-00414, Examples 1-8; Appx10642-10643 ¶¶51-52, 55.

The district court’s erroneous construction of reference claim 5 as covering a “genus” of glycosylated and non-glycosylated aflibercept rested primarily on its belief that construing the claim to exclude non-glycosylated species would render superfluous the express requirement *in the ’865 patent claims* that the VEGF antagonist “is glycosylated.” Appx00086. But as this Court has explained, the same invention may be claimed in different ways. *See Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1480 (Fed. Cir. 1998) (“[C]laims that are written in different words may ultimately cover substantially the same subject matter.”). Further, “[a]lthough [it] ha[s] in some instances interpreted claim terms to avoid redundancy, the rule is not inflexible.” *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1371 (Fed. Cir. 2017).

Here, the intrinsic and extrinsic evidence compels the conclusion that, while the claims of each patent may use different language to describe it, both refer to the only VEGF antagonist disclosed and tested

in the specification: aflibercept. *Multiform Desiccants*, 133 F.3d at 1480; *see also Inpro II Licensing, S.A.R.L. v. T-Mobile USA, Inc.*, 450 F.3d 1350, 1354 (Fed. Cir. 2006); *see also* Appx10688 ¶172, Appx10690-10692 ¶¶177-80, Appx10698 ¶204, Appx10703-10704 ¶¶223-24.

b. Even if reference claim 5 refers to a “genus” of glycosylated and non-glycosylated “species,” it still anticipates the glycosylated “species”

Even accepting the district court’s construction of reference claim 5, the glycosylation limitation would not distinguish the asserted claims. The district court determined that a POSA would have understood claim 5’s “VEGF trap consisting of amino acids 27-457 of SEQ ID NO:4” as including both glycosylated and non-glycosylated species of aflibercept, a genus of two. Appx00085-00088. Where a POSA is able to envision all species that lie within a “genus” claim, that genus anticipates the species. *See In re Petering*, 301 F.2d 676, 681-82 (C.C.P.A. 1962); *see also AbbVie, Inc.*, 764 F.3d at 1379; *Titanium Metals Corp. of Am, v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985). That is plainly true here.

At a minimum, a POSA would have been able to envision from the court’s “genus” at least the broader “species” claims of the ’865 patent “wherein said VEGF antagonist fusion protein is glycosylated.” *See*

Petering, 301 F.2d at 681 (holding that if a POSA can envision a species that lies within a “genus” claim, the genus anticipates that species).

A POSA would have also been able to envision a “species” glycosylated at asparagine residues 62, 94, 149, 222, and 308 after examining the specification, which may (and indeed must) be used to determine the meaning and scope of claim terms. Testimony from Dr. Tessier established that a POSA looking into the specification to understand the meaning and scope of the term “VEGF trap consisting of amino acids 27-457 of SEQ ID NO:4” would have examined SEQ ID NO:4 and discerned that this amino acid sequence contains five N-linked glycosylation consensus sequences at asparagine residues 62, 94, 149, 222 and 308. Appx10684-10687 ¶¶163-70. The POSA would have been aware that mammalian cells such as CHO cells “read” these consensus sequences to understand where to attach glycan moieties to a glycoprotein. Appx10662 ¶99. From this common knowledge, the POSA would have immediately envisioned that one species within the purported claim 5 “genus” is glycosylated at all five of these consensus sites. Appx10692-10693 ¶¶181-83, Appx10698-10699 ¶¶205-06.

The specification may also be used in an ODP analysis to gauge which species were known and intended to fall within the meaning of the earlier-filed claims. *See 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”). As explained, the specification expressly teaches that the “VEGF trap consisting of amino acids 27-457 of SEQ ID NO:4” is glycosylated at asparagine residues 62, 94, 149, 222, and 308 as required by claims 14 and 39.

Even if the district court was correct to place blinders on the POSA to prevent any scrutiny of the specification, the POSA would not have been blind to the prior art. “[S]pecies 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). It is undisputed that a POSA would have known from Regeneron’s prior-art *Daly* reference that aflibercept constituted “amino acids 27-457 of SEQ ID NO:4” and is glycosylated at asparagine residues 62, 94, 149, 222, and 308. Appx10663-10667 ¶¶103-09 (citing Appx07781 ¶13, Appx07788 ¶64; Appx07790 Example 8 and

¶84), Appx10693-10694 ¶184 (citing Appx11772), Appx10708-10709 ¶238. Thus, *Daly* would have enabled the POSA to envision this species.

c. At a minimum, Celltrion raised a substantial argument that the use of aflibercept, with its glycans intact, would have been an obvious choice

Even if reference claim 5 does not anticipate the glycosylation limitations of the asserted claims, it plainly renders them obvious as a matter of law. Assuming a POSA would understand the claim to be directed to a “genus” of glycosylated and non-glycosylated “species,” the very text of the claim teaches the use of a glycosylated species as much as it does a non-glycosylated one. The court’s holding that a glycosylated species would not have been obvious to a POSA cannot be reconciled with its own view of how a POSA would understand the claim. Further, while “[a] species contained in a previously-patented genus may be patentable if the species manifests unexpected properties or produces unexpected results,” *AbbVie*, 764 F.3d at 1380, that cannot be said of the court’s glycosylated “species” here:

1. This Court has made clear that in an ODP analysis, the specifications of the earlier-and later-expiring patents may be consulted to understand whether a later-claimed species has beneficial properties

or a utility that were unexpected from the earlier patent's disclosure. *See AbbVie*, 764 F.3d at 1381.

Here, the two patents are generally directed to “[s]table formulations of a VEGF-specific fusion protein antagonist.” *E.g.*, Appx08283, 1:62-63. Examples 3 and 4 report the stability of the reference claim 5 formulation made using intact, glycosylated aflibercept, the alleged “species” claimed in the ’865 patent. The stability reported in Examples 3 and 4 indisputably is the same as that claimed in the ’865 patent. There was nothing unexpected about this result.

There was also nothing unexpected about the suitability using intact, glycosylated aflibercept to make a formulation for intravitreal administration. Reference claim 5 states on its face that its formulation is a “stable ophthalmic formulation” that is “suitable for intravitreal administration.” Appx08292, 19:23-25. Assuming the claim is directed to a genus of glycosylated and un-glycosylated species, this should apply to the whole genus. Further, the title of the patent, in addition to the specification, clearly indicate that all of the disclosed embodiments of the alleged invention are “suitable for intravitreal administration.”

Appx00407, Title, Abstract; Appx00409, 1:45-52; Appx00411, 5:23-25.

There was nothing unexpected about this suitability.

2. Even if the face of claim 5 and the specification were to be ignored, intact, glycosylated aflibercept was a known, obvious species to include in reference claim 5. There was, undisputedly, only *one* protein known in the prior art with the amino acid sequence required by claim 5: aflibercept. Appx10707-10709 ¶¶235-40. As explained, *Daly* disclosed both the sequence and glycan structure of aflibercept. Appx10708-10709 ¶238 (citing Appx07781 ¶13, Appx07788 ¶64; Appx07790 Example 8 and ¶84, Appx11772). With only one option to choose from, selecting aflibercept for use in claim 5 would have been blindingly obvious.

A POSA would have been reassured in using this singular option by the fact that Regeneron had already presented successful clinical trial results for aflibercept as an intravitreal treatment. Appx10715 ¶252 (citing Appx12002, Appx11957, Appx11975); Appx10656 ¶85; Appx10707-10708 ¶¶236-37 (citing Appx07282). Regeneron had also published a wealth of data about the superior *in vivo* performance of aflibercept, including a superior safety over other VEGF antagonists. Appx10655-10658 ¶¶84-92; Appx10707-10709 ¶¶236-38.

3. The district court based its finding that a POSA would not have regarded the use of intact, glycosylated aflibercept to have been an obvious choice almost entirely on its view that certain prior-art references “taught away” from the use of aflibercept.

“[T]eaching away is a demanding standard, requiring distinctly negative teachings that go beyond even expressing a preference for an alternative.” *In re Samuels*, No. 2021-2166, 2024 WL 960453, at *3 (Fed. Cir. Mar. 6, 2024) (non-precedential). The prior art does not teach away from a known, workable option simply because it teaches that there are better or preferred options. *See Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017). Instead, “a reference teaches away when it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant.” *Id.*; *Galderma Labs, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). The degree of teaching away must also be weighed against the teachings of the prior art *as a whole*. *See Arctic Cat Inc. v. Bombardier Rec. Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017).

Here, the district court found that the prior art taught away from using intact, glycosylated aflibercept based on purported concerns that it

(1) could not penetrate the retinal barrier; (2) had an increased half-life; and (3) would cause intra-ocular inflammation. Each conclusion rests on reversible legal and factual error.

First, the district court found that prior art taught away from glycosylation because glycosylation increases the size of the molecule beyond the supposed 77 kDa “exclusion limit” for penetrating the retina. Appx00093. But the district court ignored that reference claim 5 itself teaches that a VEGF antagonist with a higher molecular weight than this “exclusion limit,” may be used in a formulation “suitable for intravitreal administration.” Appx10675 ¶128, Appx10679-10680 ¶153, Appx10688 ¶172; Appx10714-10715 ¶251.

Reference claim 5 is limited to the use of a VEGF antagonist with the amino acid sequence of aflibercept. The prior art disclosed that aflibercept “is a dimeric glycoprotein with a protein molecular weight of 97 kDa and contains ~15% glycosylation to give a total molecular weight of 115 kDa.” Appx11772 ¶36; Appx10714-10715 ¶251. A molecular weight of 97 kDa is significantly higher than 77 kDa. To the extent the district court viewed the ’865 patent as claiming the “discovery” that a VEGF trap with a molecular weight greater than 77 kDa may be used in

an ophthalmic formulation suitable for intravitreal administration, reference claim 5 teaches that discovery. Appx10714-10715 ¶251. The court erred as a matter of law in ignoring these teaching.³

The district court compounded this error by relying exclusively upon prior art that does not pertain to aflibercept. *Ghate* and *Jackson*, on which the court primarily relied, do not concern aflibercept or any protein that is structurally similar to aflibercept. Appx07263-07276, Appx07285-07290. As Dr. Tessier explained, a POSA would have understood that the molecules tested in *Ghate* and *Jackson* had structures and properties different than aflibercept and thus the reported results were not indicative of how aflibercept would perform.

³ The district court also relied on the testimony of Dr. Trout from the *Mylan* litigation in concluding that a POSA would not have been motivated to use glycosylated aflibercept given glycosylation increases the size of the molecule decreasing retinal penetration. Appx.00093. In citing the *Mylan* decision, the district court relied on the proposition that “[s]ubstantial weight may be given to a patent’s litigation history in connection with a motion for relief pendente lite” (Appx.00039 (quoting *H.H. Robertson, Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 388 (Fed. Cir. 1987) *abrogated on other grounds by Markman v. Westview Instruments*, 52 F.3d 967 (Fed. Cir. 1995)). The court’s reliance on *Mylan* was legal error because the case below and *Mylan* did not “*includ[e] similar issues of fact and law.*” *H. H. Robertson*, 820 F.2d at 388 (emphasis added); see also *Atlas Powder Co. v. Ireco Chemicals*, 773 F.2d 1230, 1232 (Fed. Cir. 1985).

Appx10716-10720 ¶¶255-64. Additionally, the papers acknowledged their own shortcomings. For example, *Jackson* explicitly states that the reported exclusion limit pertains to whether molecules can “freely diffuse” across the fixed human retina, *i.e.*, flow without any resistance at all, as opposed to being unable to penetrate the retina. Appx10720-10721 ¶¶265-66 (citing Appx07285). A POSA would not have interpreted these data as teaching that molecules with the molecular weight, glycosylation, and shape of aflibercept could not significantly penetrate the retina. *Id.* The district court failed to address this un rebutted evidence.

The district court also ignored the evidence and testimony offered by Dr. Tessier that Regeneron had presented successful clinical trial results for intact, glycosylated aflibercept as an intravitreal treatment in 2006, as explained. *Supra*, 49; *see also* Appx10722 ¶270. This was after *Ghate* and *Jackson* were published. Regeneron did not present any evidence rebutting Dr. Tessier’s testimony in this regard. The court also discounted Dr. Tessier’s un rebutted testimony regarding *Rosenfeld* (Appx00094-00095), which also post-dates *Ghate* and *Jackson* and teaches that the glycosylated antibody bevacizumab, having a molecular

weight of 149 kDa—larger than that of aflibercept—was effective when administered intravitreally. Appx11673-11677; Appx10715-10716 ¶254. While the district court credited Regeneron’s expert Dr. Trout on “teaching away,” it was not free to ignore Dr. Tessier’s unrebutted testimony and evidence. *See Bayer*, 874 F. 3d at 1324 (“a district court cannot, through a credibility determination, ignore the wealth of evidence, especially as in this case where the [patentee’s] expert did not even address it.”).

Second, the court concluded that a POSA would have been discouraged from using intact, glycosylated aflibercept because glycosylation increases serum half-life, and the *Daly* reference purportedly taught that a shorter serum half-life was desirable. Appx00095. *Daly* does not teach away. To the contrary, *Daly* suggests the use of intact, glycosylated aflibercept, since that is the only “species” of VEGF trap disclosed that meets the amino acid sequence requirements of claim 5. Appx07788 ¶64; *see also* Appx10653-10655 ¶¶81, 83; Appx10660-10661 ¶96; Appx10663-10664 ¶¶103-04; Appx10667 ¶109; Appx10707 ¶235. And although *Daly* states that smaller glycosylated and non-glycosylated “mini-traps” have “optimized characteristics for

local/intravitreal delivery, i.e., a shorter serum half-life for faster clearance and minimizing unwanted systemic exposure,” Appx07785 ¶43, it does not teach that intact, glycosylated aflibercept *could not be used* to make the intravitreal formulation of claim 5 because of its half-life. Appx10721-10722 ¶¶267-70. Indeed, the disclosed “mini-traps” are irrelevant given that claim 5 taught that *full-length* aflibercept could be used intravitreally. The district court also did not weigh *Daly* against Dr. Tessier’s testimony that a POSA would have known that Regeneron had put intravitreal aflibercept into clinical trials.

Third, the district court found that *Daly* “taught away” from the use of intact, glycosylated aflibercept in claim 5 because a POSA at the time of the invention purportedly would have been concerned that the “Fc” region of the aflibercept amino acid sequence, which in antibody molecules can play a role in the body’s natural immune response, would cause intra-ocular inflammation. Appx.00097-00098. Once again, the passage in *Daly* cited by the court simply does not make that conclusion; it merely taught a method by which the functioning of the Fc region could be reduced if desired. Appx07784 ¶38. Regardless, claim 5 itself teaches that a VEGF trap with an Fc region may be used in a formulation that is

“suitable for intravitreal administration,” since “amino acids 27-457 of SEQ ID NO:4” indisputably contain an Fc region. *See, e.g.*, Appx08747-08749 (showing FcΔc1(a) region at amino acids 232-457). The court’s conclusion that this lone passage in *Daly* “taught away” is entirely unsupported, especially in light of Regeneron’s published safety data and intravitreal clinical trial.

3. Describing the inherent stability of the reference claim 5 formulation in the ’865 patent claims does not render them patentably distinct

The district court was also wrong to conclude that the stability limitations added to the asserted claims distinguished them from reference claim 5. In fact, they are nothing more than a description of the inherent stability of the claim 5 formulation explicitly reported in Examples 3 and 4. Claim 5’s requirement that its formulation be “stable for at least 4 months” expressly anticipates the stability limitations in the asserted claims, and the ingredients in its formulation inherently anticipate them. The district court’s contrary conclusion rested on an incomplete, flawed claim construction.

a. Reference claim 5 and the asserted claims merely describe the stability shown in Examples 3 and 4 of the common specification using different words

The district court did not construe the full phrase “at least 98% of said VEGF antagonist is present in native conformation following storage at 5 °C for two months as measured by size exclusion chromatography” that appears in the asserted claims. The specification also does not define, or even use, this phrase. But the common knowledge of the POSA and the intrinsic evidence make clear that the phrase defines a rate of aggregation over a particular time, under particular conditions.

It is undisputed that a POSA would have understood “native conformation ... as measured by size exclusion chromatography” to refer to un-aggregated VEGF antagonist, since SEC is a technique that is used to quantify the formation of aggregates. Appx10667-10668 ¶110, Appx10670-10673 ¶¶117-19.

And when Regeneron added the phrase “at least 98% of said VEGF antagonist is present in native conformation following storage at 5 °C for two months as measured by size exclusion chromatography” to the asserted claims to overcome the ODP rejection over the ’594 patent, Regeneron explained it referred to “the percentage of the VEGF antagonist which maintains its conformation following storage over a given period of time.” See Appx07863. Properly construed, the phrase

requires a particular degree of inhibition of aggregation over time during storage: no more than 2% of the VEGF trap may aggregate over a two-month period when stored at 5 °C.

With the claim properly construed, it cannot be disputed that the formulation of reference claim 5 inherently meets this claim limitation. As explained, Examples 3 and 4 of the specification assessed the propensity of the claim 5 formulation to form aggregates over time when stored at 5 °C in vials and PFS. *Supra*, 11. The data in those examples show that, whether presented in a vial or PFS, less than 2% of the VEGF trap initially present had aggregated at the two-month mark, and in fact, less than 1% at the two-month mark as required by asserted claims 16 and 41. *Id.* These examples also show that the claim 5 formulation meets the claimed turbidity of claims 15 and 40. The data in Example 1 similarly demonstrated less than 2% of the VEGF trap initially present had aggregated at the 24-month mark, as in claims 17 and 42. Regeneron has also repeatedly acknowledged that EYLEA, which has the same ingredients as the claim 5 formulation, has the stability of the asserted claims. *See* Appx05248-05249 ¶366; Appx05194-05195 ¶234 (citing Appx09465); *see also* Appx10667-10670 ¶¶110-15.

A POSA would not regard the requirement in reference claim 5 that the formulation be “stable for at least 4 months” as being materially different than the stability required by the ’865 patent claims. While the district court construed the term “stable” as being “broader than, and not limited to,” the storage stability recited in the ’865 patent claims, it failed to consider how a POSA would understand the scope and meaning of the full phrase “stable for at least 4 months” in light of the specification, including Examples 3 and 4. A POSA would have looked to the specification and seen that the only description of stability at four months for the claim 5 formulation is the four-month stability testing reported in Examples 3 and 4. Appx10679-10683 ¶¶153-60, Appx10688-10690 ¶173. The asserted claims merely describe the data reported in these examples.

The specification confirms that the stability of the asserted claims was not an unexpected property. *AbbVie*, 764 F.3d at 1380. As explained, that stability appears to have been lifted out of Examples 3 and 4, which use the claim 5 formulation. *See, e.g.*, Appx10694-10696 ¶¶186-92, 10699-10702 ¶¶210, 215, 218. Indeed, the asserted claims merely claim the utility of the reference claim 5 formulation. It would “shock one’s sense of justice if an inventor could receive a patent upon a composition

of matter” like the claim 5 formulation, “setting out at length in the specification” its useful storage stability, “and then prevent the public from making any beneficial use of such product by securing” a second patent claiming that useful storage stability. *See AbbVie*, 764 F.3d at 1381, n.10.

b. The district court’s erroneous conclusion finding no anticipation appears to have been based on an incorrect, implicit claim construction

The district court’s order suggests it viewed the asserted claims as limited to formulations in which “the VEGF trap” used to make those formulations had an initial purity of at least 98% (as measured by SEC) *prior to storage* under the claimed conditions. According to Regeneron, “98% native conformation is not necessarily present” in the formulation of claim 5 because “up to 10% aggregation even at time zero is both possible and preferred.” Appx16967. The court, in adopting Regeneron’s position, also relied on a fact declaration from Dr. Graham, submitted in reply, in which Dr. Graham describes a formulation of EYLEA that was made using a lot of aflibercept active ingredient in which more than 3% of the protein had aggregated prior to storage. Appx00102-00104. Unsurprisingly, this lot still had more than 3% aggregated *after* a period

of storage under conditions that differed from those of the asserted claims. According to the district court, this declaration is evidence that the claim 5 formulation does not inherently have the storage stability of the '865 patent claims, since a formulation with all the ingredients of EYLEA, like claim 5, can *start* with more than 3% of the aflibercept in aggregated form and thus will not necessarily have “at least 98%” of the aflibercept unaggregated after storage. *Id.*

This implied construction makes no sense in the context of a patent directed to formulations that are stable, *i.e.*, do not degrade over time, and is not supported by the intrinsic evidence. The claims of the '865 patent require only that “a VEGF antagonist” with the specified structure be present in the formulation, and that “the concentration of said VEGF antagonist ... is 40 mg/ml.” The claims do not otherwise limit the VEGF antagonist prior to storage. Nowhere in the specification do the inventors describe the initial purity of the VEGF antagonist as being critical to the invention. In fact, the specification makes no mention at all of the initial purity of the VEGF antagonist, other than to note that “the fusion protein is preferably substantially free of aggregates” and that “[s]ubstantially free of aggregates” means that 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.” Appx00411, 6:50-55. Far from *mandating* that the VEGF antagonist of the ’865 patent claims have less than 2% aggregates present prior to storage, the specification suggests that the VEGF antagonist only *preferably* contains *less than 10%* aggregates prior to storage. The asserted claims require only that the formulation be sufficiently stable so that no more than 2% of whatever un-aggregated VEGF antagonist is present prior to storage aggregate during the claimed storage period.

The district court’s construction is also at odds with its post-trial findings of fact in the *Mylan* case as to enablement, which concluded that EYLEA met all of the stability limitations of the claims of the ’865 patent and that no evidence of record established that any 40 mg/ml formulation of aflibercept which contained the buffer, stabilizing agent, organic co-solvent and pH described in the ’865 patent claims fell outside of the claims’ stability limitations. *Regeneron Pharms.*, 2024 WL 382495 at *67; *see also* Appx10695 ¶188; Appx05248-05249 ¶366.

c. Even if the district court's construction were correct, it would have been obvious to use highly pure aflibercept to make the reference claim 5 formulation

Even assuming that the claims of the '865 patent require the VEGF antagonist to have an initial purity of at least 98% and reference claim 5 does not, this is still not a patentable distinction. The specification assumes achieving this initial purity is within the ambit of routine skill, since it does not provide guidance on how to accomplish it. *E.g.*, Appx00411, 6:40-58. Unrebutted testimony from Dr. Tessier established that a POSA would have been motivated to make proteins for therapeutic use, such as aflibercept, at least 98-99% pure before using them to make a therapeutic formulation like that of claim 5. Appx10645 ¶61, Appx10648-10650 ¶¶67-72, Appx10723-10724 ¶¶271-73.

The perils of adopting Regeneron's 120-page proposed order in its entirety is demonstrated here by the fact that the district court granted Celltrion permission to file a sur-reply to make this obviousness argument, Appx00181, but mistakenly left in Regeneron's proposed finding that Celltrion "waived this argument by not relying on it in its Opposition." Appx00112. Not so. By stating the argument was "considered herein" on the merits, the district court explicitly recognized

the argument as part of the record. Appx00113. And rightly so because Regeneron first raised this issue in its reply in support of its motion for preliminary injunction such that Celltrion could only address it in a sur-reply.

At this preliminary stage, Celltrion has raised at least a substantial question that the stability limitations of the asserted claims do not render them patentably distinct over reference claim 5.

4. pH does not distinguish reference claim 5 from the asserted claims

Lastly, while the district court found that the pH of the claim 5 formulation is not the same as the formulations of the '865 patent, this too was legally erroneous. The asserted claims, at their narrowest, require a pH of “about 6.2-6.3.” *See* claims 9 and 34. A POSA would have understood “about” to mean that the claim encompasses some variability around the claimed range. Appx10725 ¶280. Regeneron’s expert Trout conceded this point, testifying that “about” in the claims meant “approximately.” Appx12757, 150:14-21. According to Dr. Tessier’s un rebutted testimony, a POSA would have interpreted “pH 6.2-6.4” in claim 5 as lying within the pH range of “about 6.2-6.3” in the '865 patent claims. Appx10725 ¶280. Claim 5 therefore anticipates the pH

limitations of the '865 patent claims. *See* Appx10679 ¶152, Appx10696-10697 ¶¶192, 198, Appx10725 ¶280, Appx10732 ¶308.

5. Objective Indicia Do Not Support Patentability

The district court concluded that objective indicia supported the nonobviousness of the asserted claims. Appx00118. Such evidence is irrelevant to Celltrion's substantial showing of anticipation. *See, e.g., Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377 n.1 (Fed. Cir. 2003). With respect to Celltrion's evidence of obviousness, the district court's conclusion was clearly erroneous. First, its findings of unexpected results are contravened by the specification, as explained. Second, the court failed to consider Regeneron's secondary evidence of purported skepticism about the use of aflibercept in an intravitreal formulation in light of the closest prior art, which was claim 5. *See Bristol-Meyers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Claim 5, as explained, expressly taught its suitability in such a formulation. Appx10738-10739 ¶¶332-35. The court also wholly ignored the unrebutted evidence that aflibercept was known to be in clinical trials for intravitreal use. *Supra*, 49-56. The court also improperly relied on findings in the *Mylan* case that are not properly of

record in this case (*compare, e.g.*, Appx.00120 to Appx05245-Appx05250 ¶¶361-69). Finally, the court cites copying (Appx00118), but such evidence is generally not considered probative in the pharmaceutical context. *See Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); Appx10739-10740 ¶336.

III. The District Court Erred in Holding That It Likely Has Personal Jurisdiction Over Celltrion

The district court relied on this Court’s decision in *Acorda* for the proposition that the “minimum contacts” standard for personal jurisdiction is satisfied “where a non-resident defendant files an [ANDA] ‘for the purpose of engaging in ... allegedly wrongful market conduct in’ the forum state.” Appx00029 (quoting *Acorda*, 817 F.3d at 762-63. But as *Acorda* noted, personal jurisdiction may be defeated by demonstrating that other considerations, such as the burden on the defendant and the forum state’s interest in adjudicating the dispute, render jurisdiction unreasonable. *Id.* at 763-64. Those “other considerations” distinguish this case from *Acorda*.

This action is a classic case of forum-shopping, having no connection to West Virginia. Appx00460. Regeneron is a New York plaintiff and Celltrion is a Korean defendant. Celltrion has a complete

lack of contacts with West Virginia; it does not sell, offer to sell, market, or distribute CT-P42 in West Virginia; is not licensed to do business in West Virginia; and has never litigated in West Virginia. Appx00461. Celltrion’s service of a notice of commercial marketing (“NCM”) under the BPCIA—on which the district court relied in support of its opinion (Appx00032)—does not change the calculus because the NCM merely triggered Regeneron’s ability to take certain action against Celltrion. *See Genentech, Inc. v. Immunex Rhode Island Corp.*, 964 F.3d 1109, 1111 (Fed. Cir. 2020). It did not give rise to personal jurisdiction where Celltrion otherwise lacks sufficient contacts. Moreover, Celltrion’s manufacturing activities for CT-P42 have and will continue to take place outside of the United States. Appx00461. Accordingly, Celltrion lacks any of the contacts that the *Acorda* court relied on to find personal jurisdiction. *Id.* at Appx00469; *contra Acorda*, 817 F.3d at 763–64.

The district court misconstrued *Acorda* to hold that an ANDA or BLA submission and U.S. distribution channels are all that is needed to support personal jurisdiction (Appx00032), ignoring this Court’s reliance in *Acorda* on specific contacts that Mylan had with the forum state. Appx00032-00035); *Acorda*, 817 F.3d at 763-64. The district court’s

analysis would upend longstanding precedent and offend notions of due process. Under the district court’s reasoning, any time a foreign generic or biosimilar manufacturer files an ANDA or aBLA, jurisdiction for a resulting patent suit would be *per se* proper, and the manufacturer should “reasonably anticipate being hailed into,” in any district court, including jurisdictions such as Hawaii or Alaska. *Contra World-Wide Volkswagen Corp. v. Woodson*, 444 U.S. 286, 297 (1980); *Bristol-Myers Squibb Co. v. Superior Court of Cal.*, 582 U.S. 255, 262-63 (2017). That is not the law. *Id.*; *see also Avocent Huntsville Corp. v. Aten Int’l Co.*, 552 F.3d 1324, 1340 (Fed. Cir. 2008) (international products for sale in Alabama did not establish personal jurisdiction). Accordingly, the district court legally erred in concluding that Regeneron established a reasonable probability of demonstrating that it had personal jurisdiction over Celltrion.

IV. The District Court Erred in Finding a Nexus Between Celltrion’s Alleged Infringement and The Purported Harm to Regeneron

The district court concluded that allowing Celltrion to launch CT-P42 prior to a final decision would irreparably harm Regeneron. Appx00138. This conclusion rested on the legal error that the court could

ignore the “demand” test set forth in *Apple, Inc. v. Samsung Elects. Co., Ltd.*, which asks whether sales will be lost to an infringing product because of the infringement of the patentable features of the product, or because of un-patented, or unpatentable, features. 735 F.3d at 1364-65.

Instead of making Regeneron show that infringement of the allegedly patentable features of the ’865 patent would drive demand, the court improperly limited the nexus analysis to whether Celltrion “would [] be able to make the products proposed in its regulatory filing without infringing the asserted patent[].” Appx00166-00167. Such a simplified approach would only be appropriate where, in the court’s words, “the infringing product contains no feature relevant to consumers’ purchasing decisions other than what the patent claims.” *Id.* (quoting *Genband US LLC v. Metaswitch Networks Corp.*, 861 F.3d 1378, 1382, 1384 n.2 (Fed. Cir. 2017)). That is not what the record reflects.

The unrebutted testimony of the only commercial expert and prescribing physician to address demand was that the active ingredient, aflibercept, was responsible for prescribing decisions. Appx13134-13138 ¶¶1-3, 5-6, 9-21, Appx13145-13146 ¶¶39-41; Appx13172-13176 ¶1-16, Appx13179-13181 ¶23, Appx13192-13194 ¶¶44-48; Appx01346-01348;

Appx13315-13316. And Regeneron's commercial expert in another proceeding, Dr. Manning, testified that it was EYLEA's separately-patented dosing regimen that drove demand. Appx13197-98 ¶57; Appx14240-14244 ¶¶95-96; *see also* Appx13196-13197 ¶¶55-56; Appx13686-13688; Appx13755-13775. Based on this record, which undisputedly shows that the now-expired '594 patent is directed to the commercial EYLEA formulation Regeneron was required to show that practicing the features of the '865 patent, including the stability limitation that purportedly renders it novel over claim 5, contributes to demand.

Applying the correct test, the district court could not have reasonably concluded that Regeneron met its burden. Celltrion's experts testified that none of the allegedly patentable features of the '865 patent drive physician demand. Appx13145-13148 ¶¶39-48, Appx13194-13196 ¶¶49-53. The claimed 98% stability feature is particularly inconsequential because, as Dr. Trout conceded, 95% stability may suffice. Appx05257-05258 ¶¶386-87; Appx13195-13196 ¶52; *see also* Appx12942-12948. Although the district court concluded the patented features drove demand, Appx00169, Regeneron relied on no evidence of

its own (*see* Appx00608, n.5; Appx16972-16973), and the court’s judgment was premised on findings from the *Mylan* litigation absent from this record. In short, the evidence was clear that CT-P42 “would sell almost as well without incorporating the patented feature..., [and] even if the competitive injury that results from selling the accused device is substantial, the harm that flows from the alleged infringement is not.” *See Apple*, 735 F.3d at 1360-61.

CONCLUSION

The orders below should be reversed.

Dated: September 7, 2024

Respectfully submitted,

/s/ Robert V.
Cerwinski

Robert V. Cerwinski
Michael B. Cottler
Aviv A. Zalcenstein
Lora M. Green
GEMINI LAW LLP
40 W 24th Street,
Suite 6N
New York, NY
10010
(917) 915-8832
rcerwinski@geminilaw.com
mcottler@geminilaw.com
azalcenstein@geminilaw.com
lgreen@geminilaw.com

Jonathan Y. Ellis

Corinne S. Hockman
McGUIREWOODS LLP
501 Fayetteville Street,
Suite 500
Raleigh, NC 27601
(919) 755-6688
jellis@mcguirewoods.com
chockman@mcguirewoods.com

Michael Johnson
Matthew Freimuth
WILLKIE FARR & GALLAGHER LLP
787 Seventh Avenue
New York, NY 10019
(212) 728-8127
mjohnson1@willkie.com

Counsel for Defendant-Appellant Celltrion, Inc.

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 13,651 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: September 7, 2024

/s/ Robert V. Cerwinski
Robert V. Cerwinski

CERTIFICATE OF SERVICE

I hereby certify that on September 7, 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: September 7, 2024

/s/ Robert V. Cerwinski
Robert V. Cerwinski